NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

JULY 20, 1999

NDA 21070 FLEXERIL OTC SWITCH

SAFETY REVIEW
(MEDICAL OFFICER REVIEW
HFD-560)

ADDENDUM 10

4/14/99 Draft Medical Officer Actual Use Study and Global Safety Review for NDA 21-070 Flexeril® MR

1. The last sentence of the second paragraph on page 34 which states: "The site investigator thought that ***neither*** the patient's myocardial infarction ***nor*** death were definitely unrelated to the study medication," should be changed to read as follows: "The site investigator thought that ***both*** the patient's myocardial infarction ***and*** death were definitely unrelated to the study medication."

On page 48 of the draft review, the following changes should be made to Reviewer's Comment's 2 and 7:

2. Reviewer's Comment 2 which states: "Although cyclobenzaprine ***is known to cause*** arrhythmias, the 1 case report of death due to an myocardial infarction contained in this submission was confounded by the patient's concomitant use of cocaine and her underlying risk factors for heart disease," should be changed to read as follows: "Although cyclobenzaprine ***has been associated with*** arrhythmias, the 1 case report of death due to an myocardial infarction contained in this submission was confounded by the patient's concomitant use of cocaine and her underlying risk factors for heart disease."

3. The first sentence in Reviewer's Comment 7 which states: "Cyclobenzaprine ***is known to cause*** arrhythmias" should be changed to read as follows: "Cyclobenzaprine ***has been associated with*** arrhythmias."

4. On page 51, the table labeled "Sponsor's Table 43 - Adverse Events (AE) in the Cyclobenzaprine 10-mg Surveillance and Comparative Studies by the Number (%) of Patients" is a table created by the author of this draft review from the merger of 2 separate tables for data relating to spontaneous and elicited adverse events that were contained in the NDA submitted by the sponsor for review.

On page 72 of the draft review, the following changes should be made to Reviewer's Comment's 5 and 6:

5. The first sentence in Reviewer's Comment 5 which states: "Use of cyclobenzaprine ***is known to be*** associated with anaphylactic reactions in susceptible individuals as seen by the information given in Sponsor's Table 50," should be changed to read as follows: "Use of cyclobenzaprine ***has been*** associated with anaphylactic reactions in susceptible individuals as seen by the information given in Sponsor's Table 50."

6. The first sentence in Reviewer's Comment 7 which states: "Use of cyclobenzaprine ***is known to be*** associated with the occurrence of de novo seizures," should be changed to read as follows: "Use of cyclobenzaprine ***has been*** associated with the occurrence of de novo seizures."

MEDICAL OFFICER REVIEW
Division of Over-The-Counter Drug Products

NDA #: 21-070
NAME: Nonprescription Flexeril® MR (cyclobenzapine HCl) 5 mg Tablets
SPONSOR: Merck & Co., Inc.
Sumneytown Pike
P.O. Box 4, BLA-33
West Point, PA 19486
(215)233-7152

DRAFT

TYPE OF SUBMISSION: Commercial Pharmaceutical
DATE OF SUBMISSION: December 18,1998 **CDER**: December 18,1998
DATE OF REVIEW: April 14, 1999
REVIEWER: Rosemarie Neuner, MD, MPH
CSO: Mr. Kerry Rothschild, JD

Introduction

Cyclobenzaprine hydrochloride is a tricyclic amine salt that is structurally related to the tricyclic class of antidepressant drugs. Although this drug is structurally related to antidepressant drugs such as amitriptyline and promazine, it was found during its drug development to be a better skeletal muscle relaxant than antidepressant because of its sedative properties. Cyclobenzaprine has been marketed in the United States (U. S.) by Merck & Company since August 26, 1977 as a 10-mg strength tablet prescription tablet under the trade name, Flexeril® (NDA 17-821). (Note: The sponsor also received agency approval in 1977 to market a 5-mg strength tablet of cyclobenzaprine; however this strength was not actually marketed.) Flexeril® is currently approved as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. The recommended dose range for Flexeril® is 20 to 40 mg per day in divided doses which is not to exceed a total dose of 60 mg a day or a duration of use of more than 2-3 weeks. Generic prescription formulations of cyclobenzaprine have been available in the U. S. since 1989.

Merck & Company is now requesting agency approval to market a 5-mg strength tablet of cyclobenzaprine hydrochloride called Flexeril® MR as an over-the-counter (OTC) drug product for the following indication: the temporary relief of muscle pain or tightness of the back or neck due to strain, overuse, or minor injury. In support of this prescription to OTC switch NDA application, the sponsor has submitted for agency review the results of 13 clinical studies which evaluated the efficacy and safety of Flexeril® MR. The following table, Table 1, located on the next page, lists the 13 studies by type. A total of 2,106 patients were involved in these clinical trials and evaluable for safety. The 4 pharmacokinetics/pharmacodynamics (PK/PD) trials were reviewed by Dr. Sue Chi, staff reviewer from the Division of Biopharmaceutics (HFD-870); the 6 psychomotor studies were reviewed by Dr. Paul Andreasen, medical reviewer from the Division of Neuropharmacological Drug Products (HFD-120); and 2 of the 3 efficacy studies (Phase III trials) were reviewed by Dr. James Witter, medical reviewer from the

Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550). The review of the third Phase III trial, an actual use study, was done by this medical reviewer. The sponsor also submitted the results of a labeling comprehension study which has been reviewed separately by Dr. Kathryn Aikin, from the Division of Drug Marketing and Communications (DDMAC), HFD-40.

Table 1 - Tabular Listing of the 13 Nonprescription Cyclobenzaprine (CYC) Clinical Studies Submitted for NDA 21-070 Review by Study Type.

Protocol No.	Study Description	Dose	Duration	Tot. Enrolled/ Eval. for Safety
Clinical Pharmacology/Pharmacokinetic (PK/PD) Studies				
005	Open-label crossover study of single and multiple-dose pharmacokinetics and dose proportionality of cyclobenzaprine in young healthy volunteers.	CYC 2.5 mg, 5 mg, 10 mg	2 weeks	18
007	Open-label multiple-dose parallel study of pharmacokinetics of cyclobenzaprine in hepatically impaired patients and healthy subjects.	CYC 5 mg	1 week	24
010	Open-label multiple-dose study of pharmacokinetics of cyclobenzaprine in elderly subjects.	CYC 5 mg	1 week	12
011	Open-label crossover bioequivalence/bioavailability study of cyclobenzaprine tablets made by 2 different processes.	CYC 5 mg PO, CYC 1.25 mg IV	1 dose	24
Psychomotor Studies				
001	Double-blind, single-dose, crossover psychomotor study of cyclobenzaprine, diphenhydramine (DPH), and placebo in young subjects.	CYC 2.5 mg, 5 mg; DPH 50 mg; Placebo	1 dose	24
002	Double-blind, multiple-dose, crossover psychomotor study of cyclobenzaprine in young subjects.	CYC 5 mg; Placebo	4 days	18
003	Double-blind, single-dose, crossover psychomotor study of cyclobenzaprine, diphenhydramine, and placebo in elderly subjects.	CYC 5 mg; DPH 50 mg; Placebo	4 days	20
012	Double-blind, single-dose, crossover psychomotor study of cyclobenzaprine, diphenhydramine, clemastine, and placebo in young subjects.	CYC 5 mg; Clemastine 1 mg; DPH 50 mg; Placebo	2 days	28
014	Double-blind, multiple-dose crossover study to compare the effects of cyclobenzaprine, diphenhydramine, and amitriptyline on driving-related psychomotor skills in elderly subjects.	CYC 5 mg TID x 4 doses; DPH 50 mg, Amitriptyline 50 mg; Placebo	2 days	32
015	Double-blind, multiple-dose crossover study to compare the effects of cyclobenzaprine, diphenhydramine, and amitriptyline on driving-related psychomotor skills in young subjects.	CYC 5 mg TID x 4 doses; DPH 50 mg, Amitriptyline 50 mg; Placebo	2 days	33

Table 1 (Cont.)- Tabular Listing of the 13 Nonprescription Cyclobenzaprine Clinical Studies Submitted for NDA 21-070 Review by Study Type.

Protocol No.	Study Description	Dose	Duration	Tot. Enrolled/ Eval. for Safety
Phase III Studies				
006	Double-blind, multiple-dose, parallel-group efficacy and safety study in participants with acute skeletal muscle spasm.	CYC 5 mg, 10 mg; Placebo	1 week	737
008	Double-blind, multiple-dose, parallel-group efficacy dose-confirmation-study in participants with acute skeletal muscle spasm.	CYC 2.5 mg, 5 mg; Placebo	1 week	668
009	Open-label, multiple-dose, pattern-of-use study in participants with self-diagnosed muscle spasm.	CYC 5 mg	≤ 10 days	468

Note: Further information regarding the numbers of individuals studied, dosing, and the duration of exposure can be found in Sponsor's Tables 25 and 26 shown later in this review.

Global Safety Review

The global safety review is comprised of the following data: a review of the results from the actual use study, an over view of adverse events which occurred in the 13 clinical trials submitted in support of this application, and a cumulative review of postmarketing adverse event data associated with the use of cyclobenzaprine submitted by the sponsor, supplemented by postmarketing data from the agency's Spontaneous Reporting System (SRS) data base, and a literature review of clinical events associated with the use of cyclobenzaprine. A review of the safety data generated from the 2 efficacy studies (Studies 006 and 008) is contained in the review by Dr. James Witter, medical reviewer from HFD-550.

I. Study Review

STUDY-009: AN OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND PATTERN OF USE OF FLEXERIL® MR IN PATIENTS WITH PAINFUL MUSCLE SPASM.

This was an multi-center, open-label, nonrandomized, 7-day actual use study conducted at 15 sites across the continental U.S. The study's objectives were threefold: 1. To evaluate the patients' pattern of drug usage and compliance with directions when treating self-diagnosed painful muscle spasm with Flexeril® MR (primary); 2. To evaluate the safety and tolerability of Flexeril® MR 5-mg t.i.d. when taken according to the product label (primary); 3. To characterize the response of patient-rated clinical global impression of change in this study population (secondary).

Healthy, nonpregnant adults ≥ 18 years of age with self-diagnoses of painful muscle spasm, tightness, or soreness, due to strain, overexertion, and minor injuries to

the back or neck were recruited via various advertisements about the trial. In order to be eligible for study entry, individuals had to be willing to complete the study diary card, abstain from the use of alcohol during the study, and could not have a history of heart or thyroid disease, psychosis or recent problems with substance abuse (alcohol or drug), or pending workman's compensation or litigation due to cervical or lumbar spasm. Candidates were excluded from the trial if they had to concomitantly use a sedative, antidepressant, or tranquilizer during the course of the study. In order to closely approximate an actual use setting of an over-the-counter (OTC) product, study subjects were not physically examined to confirm the diagnosis of muscle spasm, nor was the study medication label explained to them by study personnel. The only restrictions imposed on participants were those mentioned in the WARNINGS section of the study medication label which read as follows:

Indications: For the relief of painful muscle spasm, tightness, or soreness due to recent strain, overexertion, or minor injuries of the back or neck.
DIRECTIONS:
Adults:
• Take **one tablet** every 6-8 hours.
• **Do not** exceed **3 tablets** in 24 hours.
• **Do not** take continuously for **more than 7 days**.
Children and adolescents:
• Do not give this product to anyone under 18 years of age.

WARNINGS:
Do not take Flexeril® MR if:
• you are taking antidepressant medication.
• you have a history of heart attack or heart disease.
• you have a history of thyroid problems.
Flexeril® MR may cause marked drowsiness.
• Do not drink alcoholic beverages while taking this product.
• Do not take this product if you are taking other medications that may cause drowsiness.
• Avoid driving a motor vehicle or operating machinery while taking this product.
FLEXERIL MR is not intended for the treatment of painful muscle spasm that has been present for weeks.
ALLERGY WARNING: Do not take this product it you have an allergic reaction to FLEXERIL or cyclobenzaprine HCL-containing products.

Consult a doctor before taking FLEXERIL MR if:
• you are taking sedatives or tranquilizers
• you are taking another muscle relaxant
• you are pregnant or nursing a baby
Consult a doctor if:
• your symptoms persist for more than 7 days or get worse
• you have any new or unusual symptoms.

At the baseline visit, Visit 1, individuals who agreed to participate in the study and signed an informed consent were dispensed a 10-day (30 tablets) supply of study medications and received instructions on how to fill out the study diary. All unused medications were collected at the follow-up visit, Visit 2, scheduled 8-10 days later along with the completed diary card. At Visit 2, patients were also asked to evaluate

their global response via a 5-point categorical scale (0 - worsening, 1 - no change, 2 - mild improvement, 3 - moderate improvement, and 4 - marked improvement). Study personnel were available via the telephone to answer any questions from the study participants about concomitant drug use or adverse events which occurred during the trial. The protocol did not require any restrictions on the participants activity other than those mentioned in the WARNINGS section of the test label (i.e., avoid the consumption of alcohol, driving or operating heavy machinery.)

A total of 468 participants were entered into the study. The following table, Sponsor's Table 2, lists the demographic characteristics of the subjects who participated in this trial.

Sponsor's Table 2 - Baseline Demographic Characteristics of Study Participants

Demographic Characteristics	Number of Participants (N=468)	(%)
Age (years): <20	**12**	**3**
20-29	**87**	**19**
30-39	**132**	**28**
40-49	**133**	**28**
50-59	**71**	**15**
60-64	**15**	**3**
≥ 65	**18**	**4**
Mean (SD)	**40**	**12.7**
Median	**40**	
Range	**18-76**	
Male	**18-76**	
Female	**18-76**	
Gender: Male	**215**	**46**
Female	**253**	**54**
Race: Caucasian	**427**	**91**
Black	**22**	**5**
Other	**19**	**4**
Method of Recruitment:		
Newspaper ad	**263**	**56**
Radio ad	**23**	**5**
Ad in pharmacy	**1**	**<1**
Ad in health club	**16**	**3**
Ad in college health center	**17**	**4**
Other	**148**	**32**

Sponsor's Table 2 (Continued) - Baseline Demographic Characteristics of Study Participants

Demographic Characteristics	Number of Participants (N=468)	(%)
Patient's Occupation[1]:		
Homemaker	21	9
Student	17	8
Managerial, Professional	49	22
Technical Support	6	3
Precision Production, Craft and Repair	4	2
Secretarial/Clerical	33	15
Retired	11	5
Service Occupations	19	8
Sales	13	6
Operators, Fabricators, Laborers	21	9
Farming, Forestry and Fishing	1	<1
Other	30	13

[1]Note: This information was collected on 225 out of 468 participants since the question was added after the study was underway.

Of the 468 participants entered into this study, the mean age was 40 years (range: 18-76 years), with the majority being female (253/468; 54%) and Caucasian (427/468; 91%). There were 18 participants ≥ 65 years of age were entered into the study. (See the above table, Sponsor's Table 2.) The greatest proportion of participants were recruited for the study via newspaper ads (263/468; 56%) followed by referrals from other sources (148/468; 32%). Since a question designed to capture occupational status was added after the study was underway, this information was gathered only on 225 out of the 468 participants (48%). The majority who answered were in managerial or professional positions (49/225; 22%) followed by individuals employed in secretarial/clerical jobs (33/225; 15%), and other positions not categorized (30/225; 13%). (Refer to Sponsor's Table 2 shown above.)

Sponsor's Table 3, found on the next page, summarizes the study participants' baseline pain characteristics. The 3 most common sources of pain were: the back (229/468; 49%), the neck (127/468; 27%), and pain arising from both the neck and the back (63/468; 14%). Although 48% (224/468) of the participants reported their pain severity as moderate in nature; pain was noted to be marked in 29% (135/468) subjects, and severe in 8% (39/468). Median duration of pain in this study was calculated to be 7 days (range: 1-99 days), with 37% (158/468) of the participants reporting that they had pain for 4-7 days prior to study entry, followed by 27% (126/468) who had pain for ≤ 3 days, and 21% (99/468) who had pain for 8-14 days. While a total of 213 out of the 468 (46%) participants enrolled in the study had a prior diagnosis of muscle spasm made by a physician, only 22% (105/468) reported using Flexeril® before study entry. After the study was started, the protocol was amended to include a question to capture the degree of participant impairment in performing usual activities due to muscle pain. Only 224 participants were asked this question, of which 41% (92/224) responded somewhat, 24% (53/224) reported very much, and 23% (51/224)

stated a little. (See Sponsor's Table 3 shown below.)

Sponsor's Table 3 - Baseline Pain Characteristics of Study Participants (N=468)

Pain Characteristics	Number of Participants (N=468)	(%)
Pain Location:		
Neck	127	27
Back	229	49
Neck and Back	63	14
Neck and Other	22	5
Neck, Back and Other	9	2
Back and Other	16	3
Other	2	<1
Severity of Pain:		
Mild	70	15
Moderate	224	48
Marked	135	29
Severe	39	8
Duration of Pain (days):		
≤ 3	126	27
4-7	158	34
8-14	99	21
>14	85	18
Mean (SD)	14	22.4
Median	7	
Range	1-99	
Prior muscle spasm diagnosed by a physician:		
Yes	213	46
No	255	54
How much has muscle pain impaired the ability to do usual activities?[1]		
Not at all	18	8
A little	51	23
Somewhat	92	41
Very much	53	24
Extremely	10	4
Previous Flexeril® MR Use:		
Yes	105	22
No	362	77
Missing	1	<1

[1]Note: This information was collected on 225 out of 468 participants since the question was added after the study was underway.

Sixty-five (65%) of the participants had secondary diagnoses of other medical aliments as shown in Sponsor's Table 4. The Musculoskeletal System was the body system with the highest percentage of reported secondary ailments (130/468; 27.8%)

followed by the Metabolic/Nutritional/Immune System (98/468; 20.9%), and the Urogenital System (84/468; 17.9%).

Sponsor's Table 4 - Summary Table of Some of the Most Commonly Reported (Incidence ≥ 1%) Secondary Diagnoses by Study Subjects Listed by Body System

Secondary Diagnoses	Number of Participants	(%)
Patients With Any Secondary Diagnosis	304	65.0
Body as a Whole	23	4.9
Cardiovascular System	53	11.3
Hypertension	37	7.9
Digestive System	63	13.5
Endocrine System	12	2.6
Diabetes Mellitus	5	1.1
Metabolic/Nutritional/Immune	98	20.9
Allergy, Nondrug	21	4.5
Allergy, Drug	57	12.2
Allergy	8	1.7
Hypercholesterolemia	12	2.6
Musculoskeletal System	130	27.8
Arthritis	21	4.5
Fracture, Vertebra	6	1.3
Strain, Back	19	4.1
Intervertebral Disc Disorder	5	1.1
Intervertebral Disc Displacement	14	3.0
Laminectomy	10	2.1
Spondylosis	5	1.1
Neck Sprain	7	1.5
Curvature of the Spine	5	1.1
Back Pain	12	2.6
Nervous System and Psychiatric	68	14.5
Headache	29	6.2
Migraine	15	3.2
Spasm	11	2.4
Respiratory System	76	16.2
Skin and Skin Appendage	19	4.1
Special Senses	7	1.5
Urogenital System	84	17.9
Menopausal Disorder	6	1.3
Menstrual Disorder	12	2.6
Hysterectomy	19	4.1
Tubal Ligation	16	3.4

Sponsor's Table 5, found on the following page, shows that two-thirds of the study cohort were currently taking medications at the time of trial entry, and lists the drugs that were reportedly taken by ≥ 1% of the participants. (Note: It is common practice to list the anti-inflammatory drugs with the analgesic drugs, but in Sponsor's Table 5, the sponsor has listed them separately.)

Sponsor's Table 5 - Summary Table of Some of the Most Commonly Reported (Incidence ≥ 1%) Background Drugs Used by Study Participants Listed by Drug Class

Drug Class	Number of Participants	(%)
Subjects With Any Prior Drug Therapy	316	67.5
Subjects Without Any Prior Drug Therapy	152	32.5
Analgesics	112	23.9
Acetaminophen	54	11.5
Acetaminophen/Hydrocodone	5	1.1
Aspirin	30	6.4
Antihistamines	10	2.1
Anti-Infectives	11	2.4
Anti-inflammatories	110	23.5
Ibuprofen	86	18.4
Naproxen	13	2.8
Autonomic Drugs	20	4.3
Atenolol	7	1.5
Cardiovascular Drugs	40	8.5
Hydrochlorothiazide/Triamterene	7	1.5
Lisinopril	8	1.7
Lovastatin	6	1.3
Cold Remedies	12	2.6
Diuretics/Electrolytes	10	2.1
Hydrochlorothiazide	6	1.3
Gastrointestinal Drugs	30	6.4
Ranitidine	5	1.1
Hormones/Synthetic Substitutes	99	21.2
Muscle Relaxants	22	4.7
Cyclobenzaprine Hydrochloride	7	1.5
Vitamins/Minerals	11	2.4
Multivitamins	5	1.1

Results:

Although 410 of the 468 (88%) participants who were dispensed study medications completed the trial, diary cards were collected from 449 participants who were included in the final study evaluations for compliance and actual use. Three (3) additional participants who failed to complete the study but answered the final global assessment question were included in the efficacy assessment of the trial. The following table, Sponsor's Table 6, shows the disposition of the participants by the reason for their discontinuation from the study. A total of 58 participants (12%) dropped out of the study prior to completing it for a variety of reasons listed below: adverse event (25; 5%), lost to follow up (16; 3%), therapy ineffective (i.e., discontinued study medications before 7-days of treatment were completed: 11; 2%), protocol deviation (3; <1%), never took study medications (2; <1%), and other (1; <1%). (See Sponsor's Table 6 shown below.) (Note: Thirty-eight patients (8%) who experienced resolution of their muscle spasm < 7 days were counted as study completers.)

Sponsor's Table 6 - Accounting of Participants Enrolled in Protocol No.009 - Actual Use Study

Disposition	Number of Participants	(%)
Total Entered/Evaluable for Safety	468	100
Total Completed[1]	410	88
Total Who Returned Diary Cards	449	96
Total Who Answered Global Assessment	452	97
Total Discontinued:	58	12
Clinical Adverse Event	25	5
Lost to Follow Up	16	3
Therapy Ineffective (discont. therapy prior to 7 days)	11	2
Protocol Deviation	3	1
Never Took Therapy	2	<1
Other	1	<1

[1]Participants who "completed study" included: 1. Those who completed the 7-day course of therapy; 2. Those who discontinued therapy prior to 7-days due to resolution of spasm.

Although 16 participants were lost to study follow up, 14 did not return their diary cards, but 2 of them (Subjects AN4396 and AN 4576) did answer the global efficacy question, and thus were included in that final efficacy analysis. The 3 participants who were classified as protocol deviations (Subject AN 4015 - a physician who took the study medication as needed; Subject AN 4509 - was on background antidepressants which were continued during the study; and Subject AN 4331 - participated in another cyclobenzaprine study within the 2-year period prior to this study) were included in the efficacy and safety analyses of the trial. Subjects AN 4330 and AN 4489 never took the study medications since the muscle spasms had disappeared before the former could

start them, and the latter subject was diagnosed with an ulcer, and thus decided against taking the study medications. These 2 patients were only included in the safety analysis of the study. One participant (Subject AN 4564) who did not complete the study was classified as "other" since he had lost both his diary card and study medications after starting the medication. However, this patient was included in both the efficacy and safety analysis because he answered the global efficacy question.

Compliance:

A total of 329 out of the 449 participants (73%) who returned the diary card at the completion of the trial were found to be compliant on analysis of the study data. The following table, Sponsor's Table 7, lists the numbers and reasons for noncompliance with study medication.

Sponsor's Table 7 - Tabular Summary of Reasons for Noncompliance by Participant Enrolled in Protocol 009 - Actual Use Study

Reason	All Participants (N=449)		Participants Who Experienced Somnolence (N=150)		Participants Who Had Taken Flexeril Previously (N=100)	
	n	(%)	n	(%)	n	(%)
Compliant	329	(73)	119	(79)	71	(71)
Noncompliant for Any Reason[1]	120	(27)	31	(21)	29	(29)
Took >3 Tablets on at Least 1 Day	60	(13)	19	(13)	14	(14)
Took > 1 Tablet/Dose at Least Once	49	(11)	12	(8)	13	(13)
Medicated TID for 8, 9, or 10 Consecutive Days	38	(8)	7	(5)	11	(11)

[1]Note: Some participants were noncompliant for more than 1 reason. Thus the numbers and percentages given for each individual reason are not additive for the sum total.

The sponsor also classified participants as being compliant if they used study medication for ≥ 8 days provided they dosed on nonconsecutive days or used less than the maximum recommended daily dose. Due to the manner in which the diary cards were designed, participants who took their last dose after midnight were credited as if they had taken it the following day. Thus, there were 15 participants in the study who were classified as being "noncompliant" since it appeared that they had taken 4 doses within a day which may have artificially inflated the noncompliance rate for any reason (27%) by 4% points. The sponsor also looked at the compliance rates of 2 subsets of participants enrolled in the study: individuals who had experienced somnolence as an adverse event while participating in the study and those who had taken Flexeril®

previously. Participants who reported experiencing somnolence during the course of the study were slightly more compliant (79%) as compared to the compliance rates for all participants (73%) and those who had taken Flexeril® previously (71%). Although the percentages of participants who took > 3 tablets on at least 1 day were nearly the same for the 3 groups, the group of participants who had used Flexeril® in the past had higher incidence rates for taking more than 1 tablet/dose at least on one occasion (13%) and medicating TID for 8, 9, 10 consecutive days (11%), as compared to the study population overall (11% and 8% respectively) and those who had experienced somnolence (8% and 5% respectively). (Refer to Sponsor's Table 8 shown above.)

The sponsor also looked at compliance by calculating each participant's percentage of noncompliant days. This data is shown in the following table, Sponsor's Table 8. Thirty-eight out of the 120 participants were classified as being noncompliant on the basis of their overall use of medication (i.e., those who medicated themselves for 8, 9, or 10 days). These participants were not included in the analysis shown in Sponsor's Table 8, which showed that 69 out of these 82 patients were noncompliant (i.e., took more tablets per day or per dose than recommended) on ≤ 50% of the treatment days.

Sponsor's Table 8 - Summary of Noncompliance by Day: Percentage of Days When Participants Were Noncompliant.

Percent of Treatment Days Noncompliant	Number of Noncompliant Participants	Percent of Noncompliant Participants	Cumulative Percentage
0-25%	52	63%	63%
26-50%	17	21%	84%
51-75%	6	7%	92%
76-100%	7	9%	100%
Total[1]	82		

[1]This table excludes the 38 participants who were noncompliant because they medicated TID for 8, 9, or 10 days.

Participant Use Analysis:

This analysis is of actual use data generated during the course of study that was recorded on the 449 diary cards handed in at the end of the study at Visit 2. (Note: In order to verify the accuracy of the information recorded on each study diary card, the sponsor compared the number of pills returned at the end of the trial with the usage information recorded by the participants in their diaries. Ninety-six percent (96%) of the participants were found to have a difference of ≤ 2 pills on this verification analysis.)

Sponsor's Table 9, shown below, demonstrates that 84 out of the 449 participants (44%) who handed in their diary cards took at least 1 tablet of study medication for ≤ 7 days [Mean (SD): 7.4(2.5) days; Range: 1-15 days] as per the

labeled dosing instructions. (Note: These were not necessarily consecutive days. Visit 2 was scheduled to occur on Study Day 8 to 10. Some participants did not return until Study Day 15.) Fifty-four percent (215/449; 54%) of the participants continued to take at least 1 tablet of the study medication for an additional 3 days beyond the recommended label duration for dosing. (Note: The participants were only dispensed a 10-day supply of study medications.)

Sponsor's Table 9 - Number of Treatment Days (N=449).

No. of Treatment Days	No. of Participants	Percentage	Cumulative %
1	13	3%	3%
2	10	2%	5%
3	17	4%	9%
4	25	6%	14%
5	20	4%	19%
6	27	6%	25%
7	84	19%	44%
8	116	26%	69%
9	57	13%	82%
10	42	9%	92%
11	30	7%	98%
12	5	1%	99%
13	0	0%	99%
14	1	<1%	100%
15	2	<1%	100%
Mean (SD) **Median**	7.4(2.5) 8		

The following table shown below, Sponsor's Table 10, shows that 75 out of 449 participants (49%) took at least 1 tablet of study medications consecutively for ≤ 7 days [Mean (SD): 6.9 (2.8) days; Range: 1-15 days] as per the labeled dosing instructions for the study medications. An additional 44% (199/449) of the participants continued to take at least 1 tablet of the study medications consecutively for ≤ 10 days. The distribution of the subject use data for these analyses are similar as seen in both Sponsor's Tables 9 and 10. (See Sponsor's Tables 9 and 10).

Sponsor's Table 10 - Maximum Number of Treatment Days (N=449).

No. of Consecutive Treatment Days	No. of Participants	Percentage	Cumulative %
1	21	5%	5%
2	27	6%	11%
3	22	5%	16%
4	30	7%	22%
5	27	6%	28%
6	16	4%	32%
7	75	17%	49%
8	109	24%	73%
9	51	11%	84%
10	39	9%	93%
11	25	6%	98%
12	4	1%	99%
13	0	0%	99%
14	1	<1%	100%
15	2	<1%	100%
Mean (SD) **Median**	6.9(2.8) 8		

The sponsor also looked at the number of treatment days by the baseline duration of muscle spasm. As demonstrated in the following table, Sponsor's Table 11, the distribution and mean of treatment days by baseline duration of muscle spasm was similar for between group comparisons of participants with muscle spasm for 0-7 days [Mean (SD): 7.2 (2.5) days], >7 days [Mean (SD): 7.8 (2.4) days], 0-14 days [Mean (SD): 7.4 (2.5) days], and >14 days [Mean (SD): 7.6 (2.4) days] duration. Although the data distribution shown in Sponsor's Table 11 is also similar to the data distributions displayed in Sponsor's Tables 9 and 10 (shown above) for the number of treatment days and consecutive number of treatment days, more participants took at least 1 tablet of study medication for $\leq$ 8 days when looking at the usage data by baseline duration of muscles spasm for the following 4 groups: 0-7 days (68/273; 25%), > 7 days (48/176; 27%), 0-14 days (94/369; 25%), and > 14 days (22/80; 28%) as compared to the patterns of usage in Sponsor's Tables 9 and 10.

Sponsor's Table 11 - Number of Treatment Days By Baseline Duration of Muscle Spasm

No. of Treatment Days[1]	Duration of Muscle Spasm			
	0-7 Days (N=273) n(%)	>7 Days (N=176) n(%)	0-14 Days (N=369) n(%)	>14 Days (N=80) n(%)
1	9(3)	4(2)	11(3)	2(2)
2	9(3)	1(1)	10(3)	0(0)
3	11(4)	6(3)	13(4)	4(5)
4	18(7)	7(4)	21(6)	4(5)
5	13(5)	7(4)	16(4)	4(5)
6	16(6)	11(6)	23(6)	4(5)
7	50(18)	34(19)	69(19)	15(19)
8	68(25)	48(27)	94(25)	22(28)
9	37(14)	20(11)	48(13)	9(11)
10	24(9)	18(10)	34(9)	8(10)
11	16(6)	14(8)	23(6)	7(9)
12	2(1)	3(2)	5(1)	0(0)
13	0(0)	0(0)	0(0)	0(0)
14	0(0)	1(1)	1(<1)	0(0)
15	0(0)	2(1)	1(<1)	1(1)
Mean (SD) Median	7.2(2.5) 8	7.8(2.4) 8	7.4(2.5) 8	7.6(2.4) 8

[1]Treatment days (days when participant took at least 1 tablet) are not necessarily consecutive.

Pill counts were performed on all returned study medication and the total number of tablets taken was calculated for each participant. Sponsor's Table 12, shown on the following page, lists the total number of tablets taken by participants enrolled in this study. Keeping with the labeled dosing instructions of 1 tablet three times a day, 70% of the participants took 21 or fewer tablets [Mean (SD): 17(8.0), Range: 1-30 tablets].

Sponsor's Table 12 - Total Number of Tablets Taken by Participants in Study No. 009 (N=449).

Tot. No. of Tablets Taken	n	%	Cumulative %
1	6	1	1
2	9	2	3
3	12	3	6
4	13	3	9
5	9	2	11
6	12	3	14
7	15	3	17
8	7	2	18
9	15	3	22
10	18	4	26
11	13	3	29
12	12	3	31
13	10	2	34
14	9	2	36
15	17	4	39
16	9	2	41
17	14	3	45
18	12	3	47
19	20	4	52
20	28	6	58
21	54	12	70
22	22	5	75
23	23	5	80
24	18	4	84
25	10	2	86
26	7	2	88
27	10	2	90
28	10	2	92
29	7	2	94
30	28	6	100
Mean (SD)	17.0 (8.0)		
Median	19		

In an effort to spot any unusual patterns of study medication usage, the sponsor also calculated the maximum number of doses/day, the maximum number of tablets/dose, and the maximum number of tablets/dose. These calculations are seen in the following table, Sponsor's Table 13. Most of the participants (276/449; 61%) took three doses/day [Mean (SD): 2.7 (0.8), Range: 1-6 tablets/day]. Thirty-eight (38) out of the 449 participants (8%) took 4 doses/day. There was only 1 outlier who took 6 doses/day. (Refer to Sponsor's Table 13, shown below.) Although 89% (400/449) of the participants took 1 tablet/dose [Mean (SD): 1.1 (0.4): Range 1-4 tables/dose], 45 of them (45/449; 10%) took 2 tablets/dose. There were 3 outliers who took 3 (2/449; <1%)

and 4 (1/449; <1%) tablets/dose. (See Sponsor's Table 13.) Fifty-eight percent (261/449; 58%) of the participants took the instructed amount of three tablets/day [Mean (SD): 2.8 (0.8) tablets; Range 1-6 tablets/day]. There were 60 participants who took 4 or more tablets/day, out of which only 5 (<1%) took ≥ 5 tablets/day. (Refer to Sponsor's Table 13 shown below.)

Sponsor's Table 13 - Table of Maximum Doses/Day, Tablets/Dose, and Tablets/Day. (N=449)

Max. No. of Doses/Day	n (%)	Max. No. of Tablets/Dose	n (%)	Max. No. of Tablets/Day	n (%)
1	48 (11)	1	400 (89)	1	39(9)
2	86 (19)	1.5	1 (<1)	2	89 (20)
3	276 (61)	2	45 (10)	3	261(58)
4	38 (8)	3	2 (<1)	4	55 (12)
5	0 (0)	4	1(<1)	5	3 (1)
6	1 (<1)			6	2 (<1)
Mean (SD)	2.7(0.8)	Mean (SD)	1.1(0.4)	Mean (SD)	2.8(0.8)
Median	3	Mean	1	Median	3

Efficacy:

At the end of the study, 452 participants answered the global assessment of efficacy question, the results of which are shown in Sponsor's Table 14 shown below. Eighty-eight percent (397/452; 88%) had some improvement with 74% (334/452) of the participants reporting marked to moderate improvement of their muscle spasm. Only 55 out of the 452 (12.2%) participants reported that they did not improve or had some worsening of their conditions.

Sponsor's Table 14 - Participant-Rated Global Impression of Change (N=452).

	Number of Subjects	(%)
Total Responders	397	88%
Marked Improvement	172	38%
Moderate Improvement	162	36%
Mild Improvement	63	14%
No Change	53	12%
Worsening	2	<1%

The sponsor also looked at global efficacy in the following four subgroups:

compliant vs noncompliant and completers vs noncompleters, which is seen in Sponsor's Table 15, below. Although participants who were compliant had a higher incidence (132/329; 40%) of experiencing marked improvements in their muscle spasm as compared to noncompliant participants (38/120; 32%), the rates for experiencing moderate improvement for both groups were very similar and the overall rates of response (i.e., those who experienced marked, moderate, or mild improvement) were nearly identical (88% vs 87%). Overall, the participants who completed the trial had a 90% (369/410) improvement as measured by the rate of response (i.e., marked, mild, or mild improvement). In the noncompleters, 67% (28/42) had marked, moderate, or mild improvement. (Refer to Sponsor's Table 15 shown below.)

Sponsor's Table 15 - Participant-Rated Clinical Global Impression of Efficacy by Compliance and Completion of Study.

Patient-Rated Clinical Global Impression of Change	Compliant (N=329)		Noncompliant (N=120)		Completers (N=410)		Noncom-pleters (N=42)	
	n	%	n	%	n	%	n	%
Marked Improvement	132	40	38	32	163	40	9	21
Moderate Improvement	114	35	47	39	153	37	9	21
Mild Improvement	44	13	19	16	53	13	10	24
No Change	39	12	14	12	40	10	13	31
Worsening	0	0	2	2	1	<1	1	2
Responders (Marked, Moderate or Mild Improvement)	290	88	104	87	369	90	28	67

The sponsor also looked at the pattern of analgesic use by participants enrolled in the study. The distribution of analgesic use by participants in the study is shown in the next table, Sponsor's Table 16. A total of 158 out of the 449 (35%) participants who returned their diary cards reported taking concomitant analgesics during the study [Mean (SD): 3.5 (3.1) days; Range: 1-15 days], out of which 25 (16%) participants took them for $\geq$ 7 days. (Refer to Sponsor's Table 16 shown below.)

Sponsor's Table 16 - Number of Days on Which Study Participants Took Analgesics (N=158).

No. of Days on Which Analgesics Were Used	Number of Participants Who Took Analgesics	Percentage (%)
1	62	39%
2	28	18%
3	11	7%
4	13	8%
5	6	4%
6	4	3%
7	9	6%
8	9	6%
9	7	4%
10	5	3%
11	1	1%
12	2	1%
13	0	0%
14	0	0%
15	1	1%
Mean (SD)	3.5(3.1)	
Median	2	

Sponsor's Table 17 seen below demonstrates that concomitant analgesic use was fairly constant (between 13-16%) during the first 7 days after which it decreased. (Note: There may be a two-fold explanation for this finding: 1. It may be an artifact since the study was only designed to be a 7-day study and the above decrease coincides with the timing of the final visit, Visit 2, which was scheduled to occur on Days 8-10 of the study; 2. The participants' muscle spasm was self-limited and resolved ending the need for continuing analgesic therapy.)

Sponsor's Table 17 - Analgesic Use by Study Day (N=449).

Study Day	No. of Participants	Percentage(%)
1	62	14%
2	74	16%
3	62	14%
4	65	14%
5	74	16%
6	59	13%
7	62	14%
8	44	10%
9	22	5%
10	19	4%
11	5	1%
12	3	1%
13	1	<1%
14	1	<1%
15	1	<1%
23	1	<1%

The following table, Sponsor's Table 18, lists the analgesics and the number of participants who took them as concomitant therapy during the study. The most commonly used analgesics during this study were: ibuprofen (72/158; 45.6%), acetaminophen (47/158; 29.7%), and aspirin (27/158; 17.1%).

Sponsor's Table 18 - Listing of Concomitant Analgesics by the Number of Participants Who Used Them. (N=158)

Analgesic	n	(%)
Acetaminophen	47	29.7
Acetaminophen/Butalbital/Caffeine	1	0.6
Acetaminophen/Codeine	1	0.6
Acetaminophen/Hydrocodone	2	1.3
Acetaminophen/Oxycodone	1	0.6
Acetaminophen/Propoxyphene HCl	1	0.6
Anti-inflammatory, NOS	1	0.6
Aspirin	27	17.1
Aspirin, Buffered, NOS	1	0.6
Aspirin/Acetaminophen/Caffeine	5	3.2
Aspirin/Aluminum Hydroxide	1	0.6
Aspirin/Caffeine/Cinnamedrine	1	0.6
Aspirin/Citricacid/Sodium Bicarbonate	1	0.6
Aspirin/Phenacetin/Caffeine/Butalbital	2	1.3
Diclofenac Sodium	3	1.9
Flubiprofen	2	1.3
Ibuprofen	72	45.6
Indomethacin	1	0.6
Ketorolac Tromethamine	1	0.6
Nabumetone	1	0.6
Naproxen	10	6.3
Naproxen Sodium	2	1.3
Piroxicam	1	0.6
Propoxyphene Hydrochloride	1	0.6
Propoxyphene Napsylate/Acetaminophen	1	0.6
Salsalate	1	0.6
Sulindac	1	0.6
Tolmetin	1	0.6

An analysis of the participants who concomitantly used analgesics versus those who did not during the study by compliance and responder status demonstrated that the compliance and responder rates were similar for both groups as shown in the following table, Sponsor's Table 19.

Sponsor's Table 19 - Concomitant Analgesic Use by Compliance and Responder[1] Status by Number and Percentage

	Compliant (N=329)		Noncompliant (N=120)		Responder[1] (N=397)		Nonresponder[2] (N=55)	
	n	(%)	n	(%)	n	(%)	n	(%)
Any Analgesic Use:	113	34.3%	44	36.7%	137	34.5%	21	38.2%
No Analgesic Use:	216	65.7%	76	65.3%	260	65.5%	34	61.8%

[1]Responders = Mild, Moderate, and Marked Improvement on Global Efficacy Question.
[2]Nonresponders = No Change and Worsening on Global Efficacy Question.

The sponsor added two "heed to warn" questions designed to capture information regarding driving or operating machinery while taking study medication at Visit 2 after the study was underway, which resulted in only 235 participants being asked these questions. Sponsor's Table 20 summarizes the patients responses. Of those asked "Did you avoid driving," 142 out of 235 (60%) responded negatively as compared to 86 out of 235 (37%) who said yes while 7 out of 235 (3%) of those who responded to the question answered that they were nondrivers. In respond to the question "Did you avoid operating machinery," 167 out of 235 (71%) of those queried reported that they do not operate machinery, while 44 out of 235 (19%) respond yes, and 24/235 (10%) responded no to the question. (Refer to Sponsor's Table 20 shown below.)

Sponsor's Table 20 - Participant Adherence to Usage Instructions (N=235)[1].

While Taking Study Medications:	No. of Participants	Percentage(%)
Did you avoid driving?		
Yes	**86**	**37%**
No	**142**	**60%**
Don't drive	**7**	**3%**
Did you avoid operating machinery?		
Yes	**44**	**19%**
No	**24**	**10%**
Don't operate machinery	**167**	**715**

[1]Since these questions were added to the case report form after the study was started, this information was captured on only 235 participants.

The sponsor also looked at the subgroup of patients who experienced somnolence during the study to see how they responded to the warning on the label not to drive while taking the study medication. Thirty-eight percent (33/86; 38%) of participants who avoided driving while participating in the study experienced somnolence as compared to the 45 out of 142 (32%) participants who did not avoid driving despite feeling sleepy. (See the following table, Sponsor's Table 21, shown

below.)

Sponsor's Table 21 - Participants' Avoidance of Driving by Incidence of Somnolence While Taking Study Medications.

	Avoided Driving	Did Not Avoid Driving	Did Not Drive	Did Not Answer Question[1]
Experienced Somnolence:	33(38%)	45(32%)	3(43%)	69(32%)
Did Not Experience Somnolence:	53(62%)	97(68%)	4(57%)	148(68%)
Total:	86(100%)	142(100%)	7(100%)	217(100%)

[1]Includes those participants entered into the study before this question was added to the case report forms.

Safety:

Two-hundred seventy out of the 468 participants (58%) who were evaluable for safety review reported experiencing one or more adverse events. (Refer to the Sponsor's Table 22). Forty-eight percent (223/468; 48%) were judged by the investigators to have a drug-related adverse event. Only 25 out of the 468 patients (5%) had to discontinue study medication due to an adverse event. (See Sponsor's Table 22.) A complete tabular listing of the participants who were discontinued from the study due to adverse events by their reason for discontinuation can be found in Attachment I.

Sponsor's Table 22 - Clinical Adverse Experiences Summary (N=468).

	Number of Subjects	(%)
One or More Adverse Experiences	270	58%
Drug-Related Adverse Experience[1]	223	48%
Serious Adverse Event	1	0.2%
Discontinued Due to Adverse Experience	25	5%

[1]Drug-related adverse experiences include those judged to be possibly, probably, or definitely drug related by the investigator.

There was only one participant who experienced a serious adverse event while participating in the study. Subject AN 4182 was a 32-year-old female with bronchopneumonia that was being treated when she was entered into the study. She was reported to have developed metromenorrhagia after ingesting the first dose of study medication. She was subsequently hospitalized a few days later for treatment of progressively worsening pneumonia. The site investigator attributed the metromenorrhagia as being possibly related to the study medication, but the worsening respiratory infection to be definitely not drug-related.

The following table, Sponsor's Table 23, lists all of the adverse events with

incidences of ≥ 1% which occurred during the study by body system. Somnolence (32.1%) was the most commonly reported adverse event followed by dry mouth (11.5%) and headache (13.2%). (Refer to Sponsor's Table 23 shown below.)

Sponsor's Table 23 - Study Clinical Adverse Events by Body System with Incidences of ≥ 1% (N=468).

Adverse Experience	No. of Participants	Percentage (%)
Body as a Whole	43	9.2%
Asthenia/Fatigue	28	6.0%
Pain, Abdominal	5	1.1%
Digestive System	83	17.7%
Constipation	5	1.1%
Dry Mouth	54	11.5%
Acid Regurgitation	9	1.9%
Nausea	12	2.6%
Musculoskeletal System	15	3.2%
Nervous System & Psychiatric	205	43.8%
Headache	62	13.2%
Dizziness	18	3.8%
Nervousness	7	1.5%
Somnolence	150	32.1%
Irritability	5	1.1%
Insomnia	5	1.1%
Respiratory System	25	5.3%
Infection, Upper Respiratory	5	1.1%
Dry Throat	5	1.1%
Skin & Skin Appendages	5	1.1%
Special Senses	9	1.9%
Urogenital System	8	1.7%

[1]Note: This table contains counts of participants. Although a participant may have clinical adverse experiences in ≥ 2 body systems, the participant is counted only once in "Participants With Any Clinical Adverse Experience."

Although only 17 out of the 18 participants ≥ 65 years of age had sufficient data to be included in the safety review of this study, the sponsor reviewed the data to see if any age-related adverse events had occurred. Sponsor's Table 24 lists all of the adverse events with incidences of ≥ 1% which occurred during the study by body system by age. Dry mouth (6 cases, 35.3%) and somnolence (6 cases, 35.3%) were the two most commonly reported adverse events for participants ≥ 65 years of age who participated in this study.

Sponsor's Table 24 - Clinical Adverse Experiences which Occurred During the Study by Age and Body System with Incidences ≥1%.[1]

	No. (%) of Participants Age < 65 (N=451)	No. (%) of Participants Age ≥ 65 (N=17)
One or More Adverse Experiences	269(57.6)	19(58.8)
Drug-Related Adverse Experience[2]	214(47.%)	9(52.9)
Serious Adverse Event	1(0.2)	0
Body as a Whole	42(9.3)	1(5.9)
Digestive System **Dry Mouth** **Acid Regurgitation** **Nausea**	76(16.9) 48(10.6) 8(1.8) 11(2.4)	6(35.3) 7(41.2) 1(5.9) 1(5.9)
Nervous System & Psychiatric **Somnolence**	199(44.1) 144(31.9)	6(35.3) 6(35.3)
Respiratory System	24(5.3)	1(5.9)
Special Senses	8(1.8)	1(5.9)
Urogenital System	7(1.6)	1(5.9)

[1]Note: This table contains counts of participants. Although a participant may have clinical adverse experiences in ≥ 2 body systems, the participant is counted only once in "Participants With Any Clinical Adverse Experience."
[2]Drug-related adverse experiences include those judged to be possibly, probably, or definitely drug related by the investigator.

Since somnolence was the most commonly reported adverse event in this study, the sponsor looked at its severity in the 150 out of the 468 participants (32%) who reported experiencing. Only 13 participants out of 468 (3%) rated it severe, followed by 62 out of 468 (13%) participants who rated it moderate, and 75 out of 468 (16%) participants who described it as mild. (Refer to Sponsor's Table 25 shown below.)

Sponsor's Table 25 - Distribution of Somnolence by Intensity (N=468).

Severity of Somnolence	Number of Participants	Percentage of Study Population
Total Patients with Somnolence	150	32%
Severity[1]: **Mild** **Moderate** **Severe**	 75 62 13	 16% 13% 3%

[1]Severity has been defined as follows: Mild - awareness of sign or symptom but easily tolerated: Moderate - discomfort enough to cause interference with usual activity; Severe - incapacitating with inability to work or do usual activity.

Reviewer's Comments:

Demographics:

1. Seventy-seven percent (77%) of the participants enrolled in this actual use were <50 years of age; 19% were between 50-65 years of age; and 18 participants (4%) were ≥ 65 years of age. This population may not representative of the population of consumers who would potentially use this product. (Refer to Sponsor's Table 2.)

2. The majority of participants who were enrolled in this trial were caucasian. There were very few enrolled of African-American descent (22/468; 5%) or representatives of other races (19/468; 4%). (See to Sponsor's Table 2.) Thus, the validity of any conclusions regarding the product's adverse event profile in the general population are questionable.

Compliance:

3. Although the majority of patients (73%) who participated in this study demonstrated that they could take the study medication for 7-days as directed by the labeling tested, this may be an artifact due to the scheduled termination of the study at Days 8-10. (See Sponsor's Table 7.) Further, even though the majority of the participants took the study medications correctly, the duration of this study may have been too short (i.e., 7-days) and a large enough supply of study medications may not have been dispensed (i.e., each individual received a 10-day supply of only 30 tablets) to capture any information regarding potential drug abuse or "dose creep" since the numbers of patients who continued to use the drug only decreased after 8-days of dosing in relation to the timing of the exit visit, Visit 2, that was scheduled to occur on Days 8-10 of the study. (Refer to Sponsor's Tables 9, 10, 11, 12 and 13.)

4. Participants who had taken Flexeril® previously had higher incidence rates for taking > 1 tablet/dose at least once (13%), and self-medicating for 8, 9, or 10 consecutive days (11%) compared to the study population overall (11% and 8% respectively) and the subgroup who had experienced somnolence (8% and 5%). (See Sponsor's Table 7.) Thus, no valid conclusions can be drawn regarding the possibility of "over-use" in consumers who have used the drug in the past and potentially abuse, due to the small numbers of patients studied and the trial's limited length.

5. Eighty-eight percent (397/452, 88%) of the participants who participated in this trial had some improvement at the end of the study. However, the recommended duration of use for this product (i.e., 7-days) which was studied in this trial may have been too short to gain reliable efficacy and misuse information. (See Sponsor's Tables 9, 10, 11 and 14.) The peak use and decrease may in fact be artificially created by the study's design, since the timing of the peak use and the decrease coincide with the participants exit visit (Visit 2) at the end of the study.

6. Sponsor's Table 15 demonstrates that despite the short duration of this study that the various subgroups of participants who completed it demonstrated response rates between 87-90%, with the greatest response in participants with marked and moderate improvement (32-40%). Thus the duration of treatment may be correct given the self-limited nature of the indication that the sponsor is seeking but it may not be clearly shown nor captured by this study because it only was designed to study 7-days of self-treatment. This is supported by the distribution data regarding the concomitant use of analgesics shown in Sponsor's Tables 16 and 17 which only begins to decrease at Day 8 at the termination of the study. (Refer to Sponsor's Tables 15, 16 and 17, and Comment 8 above.)

7. This study was too short in duration to capture any information regarding the possibility of rebound phenomena associated with the indication being studied (i.e., muscle spasm).

Efficacy:

8. Participants who had taken Flexeril® previously had higher incidence rates for taking > 1 tablet/dose at least once (13%), and self-medicating for 8, 9, or 10 consecutive days (11%) as compared to the study population overall (11% and 8% respectively) and those who had experienced somnolence (8% and 5%). (See Sponsor's Table 7.) It is not clear from the data submitted by the sponsor if this behavior was due to an apparent lack of efficacy with the 5 mg dose tested or participants' familiarity with its effectiveness at higher prescription doses. This additional information would be useful in helping to determine the possibility of "dose creep" and consumer misuse of the product. (Note: An analysis of efficacy assessment for participants who had taken Flexeril® previously has been requested from the sponsor.)

9. The sponsor did not provide an analysis of the participants' efficacy assessment by location of spasm (i.e., the neck vs the back vs both locations). This information would be useful in determining the correct indication and labeling for this product. (Note: This data assessment has requested from the sponsor.)

10. The study protocol as designed did not ask participants to record when they experienced relief or improvement with this product on their study diary cards. Although a global evaluation was performed at the end of the study at Visit 2, capturing of this information would have been useful in determining the appropriate duration of use for this product.

Safety:

11. The participants' responses to the failure to heed labeling instructions regarding driving (i.e., 60% admitted to driving while taking the study medication despite the labeled warning not to) are worrisome and could represent a potential safety hazard in

light of the somnolence associated with Flexeril's use. (See Sponsor's Tables 19, 20 and 24.)

12. Due to the limited number of elderly participants ($\geq$ 65 years of age) who participated in this study (n=17), no valid conclusions can be drawn concerning this product's safety profile in this segment of the consumer population. (Refer to Sponsor's Table 23.)

13. Although some participants who were currently taking concomitant muscle relaxants and thyroid replacement therapy were enrolled in the study, the numbers of these patients were too small to infer any valid conclusions regarding the possibility of drug-drug interactions or other adverse events. (See Sponsor's Table 5.)

Conclusion: Although the results of this actual use study suggest that for the label tested the majority of patients $\leq$ 65 years of age could possibly safely use and tolerate this product, the limited time of the trial makes it difficult to determine if this is a true finding or one artifactually created by the protocol's self-limited duration. The study's limited length makes it difficult to determine if there exists a possibility for potential drug abuse and misuse. Safety concerns are also raised concerning this products use in the elderly and by other populations of consumers at risk for developing drug-drug interactions or metabolic side effects which were not adequately represented in this study. The failure to heed the warning not to drive while taking this medication is particularly worrisome in view of the product's potential for sedation and other centrally-mediated side effects.

II. Safety Review of Serious Adverse Events Which Occurred During the Clinical Studies

The sponsor submitted for agency review the results of 13 clinical studies which evaluated the efficacy and safety of Flexeril® MR in 2,106 patients. Table 1, found at the being of this review lists all 13 studies, the doses of cyclobenzapine HCl studied, and the number of patients evaluated in these trials. Three of the psychomotor studies (Protocol Numbers: 001, 002, 003) were conducted in the United Kingdom; the remaining 10 studies were done in the U.S. One of the U.S. investigators who participated in Protocol 008 was disqualified by the agency after an extensive investigation revealed fraudulent study data in connection with other studies. Although the data from this investigator was disqualified from inclusion in the efficacy analysis of this application, the safety review includes serious clinical adverse events reported by the 40 patients from that site while participating in the study. Since cyclobenzaprine's sedative and psychomotor effects were specifically studied in 6 of the 13 clinical trials that were reviewed by Dr. Paul Andreasen, medical reviewer from the Division of Neuropharmacological Drug Products (HFD-120), this global safety review will be limited to adverse events which were reported to have occurred in patients while participating in those trials.

In this section, drug exposure information and demographic data generated from the 13 clinical studies will be discussed first, followed by a discussion of all the serious adverse events (i.e., deaths, cancers and neoplasias, and intra-trial hospitalizations), as well as an overview of all reported (non-serious) adverse events including lab abnormalities which were reported to have occurred during the course of these studies. In addition, subgroup analyses of adverse events by gender, age and race, and information regarding both drug-disease and drug-drug interactions generated from data collected in the Phase III studies is included for completeness. A separate review of the potential for drug abuse with this product was done by Dr. Michael Klein, from the Division of Drug Abuse and Anesthetic Agents, HFD-160.

Drug Exposure:

A total of 1,632 out of the 2,106 participants who were enrolled in the 13 clinical studies conducted by the sponsor in support of this submission, were actually exposed to cyclobenzaprine, and are thus included in the evaluation of the product's safety. (Refer to Sponsor's Table 1 at the beginning of this review for the numbers of subjects who participated in each of the 13 studies, and the following table, Sponsor's Table 26.) Of the 233 subjects who were enrolled in the PK/PD and psychomotor studies, 231 received cyclobenzaprine. (See the following table, Sponsor's Table 26.). Of the remaining 1,404 evaluable participants entered into the 3 Phase III studies, there were 3 other participants who were also not treated with the drug, leaving 1,632 participants treated with cyclobenzaprine in this submission. (Refer to Sponsor's Table 26 shown below.) Due to the cross-over design of some of the studies, there are more subject exposures than the total number of subjects who were actually enrolled because some

subjects received multiple treatments. (See Sponsor's Table 27 below.) (Note: Although this information has been requested from the sponsor, it has not been received by the completion of this review.) Five individuals (3 from the PK/PD and psychomotor studies and 2 from the Phase III studies) were treated in more than 1 study thus bringing the total number of participants evaluable for safety review in the data base to 2,101. (Note: All 3 subjects and 1 of the participants received cyclobenzaprine as treatment. Therefore these 4 individuals are counted twice in the following tables, Sponsor's Tables 26 and 27.) [Note: Since the 3 Phase III studies included both individuals who were prescribed study medicine by a physician (i.e., patients) and participants in a consumer use trial the term patient will be used to denote both cohorts.]

Sponsor's Table 26 - Number of Subjects by Maximum Number of Treatment Days and Treatment Group in Nonprescription Cyclobenzaprine Clinical Studies.

Subjects	CYC All Doses	Diphen 50 mg	Amit 50 mg	Clemastine 1 mg	Placebo
PK/PD and Psychomotor Studies					
1-4 days (≤10 doses)	177	135	65	28	152
5-14 days	54	0	0	0	0
Phase III Studies					
1-15 Days	1401	0	0	0	469
Total:	**1632**	**135**	**65**	**28**	**621**

Legend: CYC=cyclobenzaprine; Diphen=diphenhydramine; Amit=Amitriptyline.
Note: Three patients assigned to receive cyclobenzaprine did not take the study medication and are not included in this table.

During the development of this application the sponsor evaluated the following 4 doses of cyclobenzaprine: 1.25 mg, 2.5 mg, 5 mg, and 10 mg. The following table, Sponsor's Table 27, lists the numbers of patients who participated in the 13 clinical trials by the dose and the duration of exposure. Most of the participants (1,160) in the safety data base were treated with the 5-mg dose, followed by the 10-mg (266 participants), 2.5-mg (265 participants), and 1.5 mg (22 participants) doses. (See Sponsor's Table 27 shown below.)

Sponsor's Table 27 - Number of Subjects/Participants Exposed to Cyclobenzaprine (CYC) by Nominal Dosages and Dosing Regimens in Nonprescription Cyclobenzaprine Clinical Studies

CYC Dose (mg)	Assigned Regimen	No. of Subjects	No. of Pts.	Total
1.25 mg	1.25 mg IV single dose	22	0	22
2.5 mg	2.5 mg single dose	24	0	24
	2.5 mg single dose, followed by 2.5 mg T.I.D. Days 8 to 14	18	0	18
	2.5 mg dose T.I.D. for 7-days	0	223	223
	Subtotal for 2.5 mg	**42**	**223**	**265**
5 mg	5 mg single dose	47	0	47
	5 mg single dose, followed by 5 mg T.I.D. Days 8 to 14	18	0	18
	5 mg T.I.D. for 4 doses	93	0	93
	5 mg T.I.D. for 10 doses	36	0	36
	5 mg T.I.D. up to 7 days[1]	36	930	966
	Subtotal for 5 mg	**230**	**930**	**1160**
10 mg	10 mg single dose, followed by 10 mg T.I.D. Days 8 to 14	18	0	18
	10 mg dose T.I.D. for 7 days	0	248	248
	Subtotal for 10 mg	**18**	**248**	**266**
Total Number of Participants Evaluable for Safety:		**233**	**1404**	**1635***

[1]Note: Some of the participants in the Actual Use Study took drug for ≥ 7 days.
*Note: There were 3 patients who did take cyclobenzaprine. Thus the total number of patients who actually received cyclobenzaprine in this safety data base is 1,632.

Demographics:

The sponsor listed the demographic characteristics of the participants in the Phase III studies separately from those in the PK/PD studies as shown in the following table, Sponsor's Table 28. The population treated with cyclobenzaprine in the Phase III studies was predominately caucasian (88.8%), female (56.1%), and 30-39 years of age [Mean (SD): 41.7(± 13.1) years; Range: 18-85]. Demographically, the cyclobenzaprine-treated patients were very similar to the placebo-treated patients for all characteristics. (See Sponsor's Table 27 shown below.) Representation of black and other minorities in both the cyclobenzaprine and placebo groups was limited [Phase III studies: CYC - Black: (109/1404; 7.8%); Hispanic: (33/1404; 2.4%); Other: (15/1,404; 1.1%); Placebo-Black (43/469; 9.2%); Hispanic: (10/469; 2.1%); Other: (5/469; 1.1%)]. The subjects enrolled in the PK/PD studies were also predominately caucasian (80.7%), but there were more males (52.8%) than females (47.2%) who participated in these studies. Although the population enrolled in the PK/PD studies was younger [20-29 years of age; Mean (SD): 41.7(±20.2) years; Range 18-82] than that of the Phase III studies,

there were more minority subjects enrolled [Black: (15/233; 6.4%); Hispanic: (22/233; 9.4%); and Other: (8/233; 3.4%)]. (Refer to Sponsor's Table 28.) A total of 141 participants ≥ 65 years of age were exposed to cyclobenzaprine in either the Phase III studies (74/1404; 5.3%) or the PK/PD trials (67/233; 28.8%).

Sponsor's Table 28 - Baseline Demographic Characteristics for Subjects/Participants in Nonprescription Cyclobenzaprine Clinical Studies.

	--------Phase III Studies--------				Clin. Pharmacology	
	CYC (N=1404)		Placebo (N=469)		Studies (N=233)	
	n	(%)	n	(%)	n	(%)
Gender:						
Male	617	(43.9%)	200	(42.6%)	123	(52.8%)
Female	787	(56.1%)	269	(57.4%)	110	(47.2%)
Age:						
<20	18	(1.3%)	5	(1.1%)	8	(3.4%)
20-29	233	(16.6%)	86	(18.3%)	99	(42.5%)
30-39	415	(29.6%)	116	(24.7%)	30	(12.9%)
40-49	363	(16.7%)	139	(29.6%)	15	(6.4%)
50-59	235	(16.7%)	75	(16.0%)	10	(4.3%)
60-64	66	(4.7%)	18	(3.8%)	4	(1.7%)
≥ 65	74	(5.3%)	30	(6.4%)	67	(28.8%)
Mean (SD)	41.7(±13.1)		41.9(±13.1)		41.7(±20.2)	
Median	40.0		41.0		33.0	
Range	18-85		18-79		18-82	
Race:						
Caucasian	1247	(88.8%)	411	(87.6%)	188	(80.7%)
Black	109	(7.8%)	43	(9.2%)	15	(6.4%)
Hispanic	33	(2.4%)	10	(2.1%)	22	(9.4%)
Other	15	(1.1%)	5	(1.1%)	8	(3.4%)

Legend: CYC=Cyclobenzaprine

Study-Related Adverse Events:

Nine hundred-five (905) of the 1,635 (55%) participants exposed to cyclobenzaprine in this safety data base reported experiencing one or more adverse events as compared to 228 of the 621 (37%) participants in the placebo-treated group. The following table, Sponsor's Table 29, shows that although nearly 788 of these 1,635 (48%) events were considered to be related to cyclobenzaprine, only 62 out of the 1,635 (3.8%) participants in the cyclobenzaprine group and 8 out of the 621 (1.3%) participants from the placebo group had to withdraw from the studies due to drug-related adverse events. A total of 4 serious adverse events were reported to have occurred during the clinical studies (3 [0.2%] in the cyclobenzaprine group and 1 [0.2%] in the placebo group), none of which were considered to be drug-related. (Refer to Sponsor's Table 29 shown below.) There was 1 death which occurred in the

cyclobenzaprine group that will be discussed in detail later in this review with the other serious adverse events.

Sponsor's Table 29 - Summary of Clinical Adverse Events in the Non-Prescription Cyclobenzaprine Clinical Studies by Number of Participants

	Cyclobenzaprine (n=1635)	Placebo (n=621)
With any Adverse Event	905(55.4%)	228(36.7%)
With Drug-Related Adverse Event	788(48.2%)	162(26.2%)
With Serious Adverse Event	3(0.2%)	1(0.2%)
With Serious Drug-Related Adverse Event	0	0
Deaths	1	0
Withdrawal Due to Adverse Events	72 (4.4%)	10 (1.6%)
Withdrawal Due to Drug-Related Adverse Events	62 (3.8%)	8 (1.3%)
Withdrawal Due to Serious Adverse Events	0	0

The next table, Sponsor's Table 30, lists the number of participants who discontinued from the clinical studies in this application due to adverse events by their assigned treatment group. Seventy-three (73) out of the 83 (88%) participants who discontinued due to adverse events did so because they were thought to be drug-related. As demonstrated in Sponsor's Table 30, the incidence of withdrawal due to adverse events appears to be directly dose-related in the cyclobenzaprine-treated population. Although there were no participants who discontinued from the studies due to adverse events related to amitriptyline or clemastine, 1 (0.7%) participant withdrew due to a drug-related adverse event due to diphenhydramine and 8 (1.3%) participants withdrew due to drug-related adverse events in the placebo group. (See Sponsor's Table 30 shown below.)

Sponsor's Table 30 - Participants Who Discontinued From the Clinical Studies Due to Clinical Adverse Events by Treatment Group

Treatment Group	Number of Participants	Number (%) of Participants Discontinued Due to Clinical Adverse Events	Number (%) of Participants Discontinued Due to Drug-Related Adverse Events[1]
CYC 2.5 mg	265	6 (2.3%)	6 (2.3%)
CYC 5 mg	1162	48 (4.1%)	41 (3.5%)
CYC 10 mg	267	20 (7.5%)	18 (6.7%)
Placebo	621	11 (1.8%)	8 (1.3%)
Diphenhydramine 50 mg	135	1 (0.7%)	1 (0.7%)
Amitriptyline 50 mg	65	0	0
Clemastine 1.0 mg	28	0	0

CYC=cyclobenzaprine
[1]Note: Considered by the investigator to be possibly, probably, or definitely drug-related.

Attachment II at the end of this review contains a detailed tabular listing by drug and dose compiled by the sponsor of all the participants in this application who discontinued from the studies due to adverse events. Nearly all of the adverse events reported by participants resolved after study medication was discontinued. As shown in the following table, Sponsor's Table 31, the most commonly cited adverse event which caused participants to discontinue due to an adverse event was somnolence at each of the 3 doses of cyclobenzaprine tested. For the proposed marketing dose of 5-mg of cyclobenzaprine, the most frequently cited reasons for discontinuing treatment in this application were: somnolence (29/1162; 2.5%), headache (9/1162: 0.8%), dry mouth (8/1162; 0.7%), dizziness (6/1162; 0.5%) and nausea (6/1162; 0.5%).

Sponsor's Table 31 - Adverse Events Reported by ≥ 3 Participants Who Discontinued From the Studies Due to an Adverse Event by Number (%) of

Participants

Adverse Event	CYC 2.5 mg N=265	CYC 5 mg N=1,162	CYC 10 mg N=267	Placebo N=621
Asthenia/Fatigue	1 (0.4%)	4 (0.3%)	3 (1.1%)	1 (0.2%)
Dizziness	1 (0.4%)	6 (0.5%)	2 (0.7%)	0
Dry Mouth	1 (0.4%)	8 (0.7%)	3 (1.1%)	0
Headache	0	9 (0.8%)	1 (0.4%)	2 (0.3%)
Mental Acuity Decreased	0	3 (0.3%)	0	0
Nausea	1 (0.4%)	6 (0.5%)	1 (0.4%)	1 (0.2%)
Somnolence	3 (1.1%)	29 (2.5%)	13 (4.9%)	3 (0.5%)

Serious Clinical Adverse Events

There were a total of 4 serious clinical adverse events and 1 death reported to have occurred in individuals participating in the 13 clinical studies. (See Sponsor's Table 32 on the following page.) These 5 cases are listed in the following table, Sponsor's Table 32, located on the next page and will be discussed in detail in this section. All five cases resulted in hospitalization.

Deaths:

The 1 death contained in the clinical safety data base occurred in an insulin-dependent, obese, 33-year-old female patient (AN 2489) enrolled in Study Protocol 008-021 who was randomized to receive study treatment with cyclobenzaprine 5 mg. On Study Day 5, she developed shortness of breath and agitation while shopping. She was subsequently admitted to an emergency room where she was noted to be combative, diaphoretic, pale and hypotensive. Laboratory testing revealed an elevated serum glucose of 450 mg/dL and widened complexes on electrocardiogram (EKG). The patient developed ventricular fibrillation and went on to cardiac arrest. Attempts to resuscitate the patient failed and she died. Post-mortem examination revealed severe atherosclerotic heart disease, thought to be worsened by her underlying diabetes, and measurable amounts of a cocaine metabolite, benzoylecgonine, at a concentration of 0.1 ug/mL, which is known to cause coronary artery vasoconstriction. (Note: At autopsy cyclobenzaprine levels were not measured.) The site investigator thought that neither the patient's myocardial infarction nor death were definitely unrelated to the study medication.

Intra-Trial Hospitalizations:

Cyclobenzaprine 2.5 mg T.I.D.: An 81-year-old female patient (AN 2325) enrolled in Study 008-003 presented on Day 2 of the study with worsening back pain. She was subsequently hospitalized and treated with intravenous fluids and another prescription muscle relaxant, Robaxin. The back pain resolved 7 days later and the site investigator thought that it was definitely unrelated to the study medication.

Cyclobenzaprine 5 mg T.I.D.: On Day 8 of Study Protocol 008-003, a 41-year-old male patient (AN 2326) presented for Visit 3 complaining of chest pain, nausea, vomiting, dizziness, diaphoresis, and near-syncope. He was hospitalized and a myocardial infarction was ruled-out. The site investigator thought that these adverse events were definitely unrelated to the study medication. (Note: A copy of the patient's EKG has been requested from the sponsor.)

Cyclobenzaprine 5 mg T.I.D.: A 32-year-old female (AN 4182) was enrolled in Study Protocol 009-007 while undergoing treatment for bronchopneumonia. After 1 dose of study medication, this patient developed metromenorrhagia and stopped taking any more of the study medication. She was subsequently hospitalized a few days later due to worsening of her underlying bronchopneumonia. The site investigator thought that the metromenorrhagia was probably related to the study medication, but the worsening of her pneumonia was definitely unrelated.

Placebo: A 56-year-old female (AN 2357) enrolled in Study Protocol 008-003 had a mammogram on Study Day 2 which demonstrated a right breast mass. On breast biopsy the mass was found to be malignant. The patient subsequently had a modified right radical mastectomy. The site investigator thought that the patient's breast cancer was definitely unrelated to the study medication.

Cancers and Neoplasias:

There was only 1 report of cancer in the safety data base submitted for review. This individual (AN 2357) randomized to placebo who was diagnosed with breast cancer during the study. (Note: See the above narrative discussion under Intra-Trial Hospitalizations and Sponsor's Table 32 below for further information.) The tumor was thought to be definitely unrelated to the patient's treatment.

Sponsor's Table 32 - Listing of All Fatal and Non-Fatal Serious Adverse Events Which Occurred in Patients Enrolled in the 13 Nonprescription Cyclobenzaprine Clinical Trials.

Study No.	Patient No.	Age/ Gender	Drug/Tot. Daily Dosage	Relative Day of Onset	Adverse Event	Duration	Intensity	Drug Relation	Action Taken	Resolved
008-021[1]	AN2489	33yo/F	CYC/15 mg	Day 5	MI Cardiac Arrest Death	93 min 1 day	Severe Severe Severe	Def. Not Prob. Not Def. Not		
008-003	AN2325	81yo/F	CYC/7.5 mg	Day 2	Pain, Back	7 days	Severe	Def. Not	None	Yes
008-003	AN2326	41yo/M	CYC/15 mg	Day 8	Pain, Chest Syncope Labyrinthitis	3 days	Severe	Def. Not	None	Yes
009-007	AN4182	32yo/F	CYC/5 mg	Day 1	Pneumonia, worsening	1 day	Severe	Def. Not	None	Yes
008-003	AN2357	56yo/F	Placebo	Day 2	Mass, Breast	17 days	Moderate	Def. Not	None	Yes

CYC=Cyclobenzaprine
[1]Note: The investigator for this site was disqualified.

Nonserious Adverse Events:

Sponsor's Table 33 shown on the next page, lists by body system all of the adverse events with incidences ≥ 1% that were reported to have occurred in participants who were taking either cyclobenzaprine or placebo in the studies conducted by the sponsor in support of this NDA. This table also shows the incidences of adverse events that were thought to be drug-related by the study investigators. In these short-term studies, participants treated with cyclobenzaprine reported more digestive system (23.2%) and nervous system/psychiatric (39.6%) adverse events compared to placebo treated patients (13.5%, and 22.7%, respectively). This is due to the higher incidence of reports of dry mouth (17.7%) and somnolence (30.4%) respectively in the cyclobenzaprine treated group compared to the placebo treated group (5.5%, and 13.0%, respectively). Cyclobenzaprine's safety profile is shown in Sponsor's Table 33.

Sponsor's Table 33 - Clinical Adverse Events[1] by Body System for all Participants in the Nonprescription Cyclobenzaprine Clinical Studies with Incidences ≥ 1% in

the Cyclobenzaprine-Treated Population by Percent of Participants and Percent Drug-Related[2]

	Cyclobenzaprine (N=1635)		Placebo (N=621)	
	% of Participants	% Drug-Related[2]	% of Participants	% Drug-Related[2]
Percent With Any Adverse Event:	55.4%	48.2%	36.7%	26.1%
Body as a Whole:	9.2%	7.3%	4.5%	3.1%
Asthenia/Fatigue	6.6%	6.2%	2.6%	2.6%
Digestive:	23.2%	21.2%	13.5%	10.8%
Acid Regurgitation	1.0%	0.6%	0.5%	0.2%
Constipation	1.4%	1.2%	1.1%	0.8%
Dry Mouth	17.7%	17.4%	5.5%	5.3%
Nausea	2.7%	2.0%	4.3%	3.5%
Musculoskeletal:[3]	3.0%	0.6%	2.4%	0.3%
Nervous System & Psychiatric:	39.6%	35.8%	22.7%	17.7%
Dizziness	3.8%	3.7%	1.8%	1.6%
Headache	8.8%	3.5%	7.1%	3.1%
Mental Acuity Decreased	1.0%	0.9%	1.3%	1.3%
Nervousness	1.0%	1.0%	0.3%	0.3%
Somnolence	30.4%	29.9%	13.0%	12.9%
Respiratory:	4.6%	0.9%	3.2%	0.5%
Infection, Upper Respiratory	1.0%	0	1.1%	0
Skin & Appendage:[3]	1.4%	0.7%	1.4%	0.6%
Special Senses:[3]	2.6%	2.1%	1.9%	1.1%
Urogenital:[3]	1.2%	0.6%	1.8%	1.0%

[1]Note: This table is based on counts of participants. Although a participant may have had 2 or more adverse events, the person is counted only once in the body system total and in "Percent with any Adverse Event."
[2]Considered by the investigator to be possibly, probably, or definitely drug-related.
[3]All individual adverse events in this body system have an incidence <1% in the cyclobenzaprine population.

As part of their comparative data analysis, sponsor also looked at the incidences of the most commonly reported adverse events (i.e., those with incidences $\geq$ 3%) from the 2 double-blind placebo-controlled studies (Protocols 006 and 008) submitted in this application. (Refer to Sponsor's Table 34.) The most commonly reported adverse events from these 2 studies were: somnolence, dry mouth, headache, asthenia/fatigue, nausea, and dizziness. With the exception of headache and nausea, the incidences for somnolence, dry mouth, asthenia/fatigue, and dizziness are dose-dependent as shown in Sponsor's Table 34. Participants treated with cyclobenzaprine 10-mg were found to have significantly higher ($p \leq 0.023$) incidences of both somnolence and dry mouth as compared to the cyclobenzaprine 5-mg, cyclobenzaprine 2.5-mg and placebo treatment groups. In addition, the group treated with cyclobenzaprine 5-mg had a significantly

higher incidence of somnolence and dry mouth as compared to the cyclobenzaprine 2.5-mg and placebo treatment groups ($p \leq 0.028$) which was also shown to be true for the cyclobenzaprine 2.5-mg treatment group when compared to the placebo group ($p \leq 0.003$). (Refer to Sponsor's Table 34 shown below.) On further analysis, the cyclobenzaprine 10-mg and 5-mg treatment groups were also shown to have significantly greater incidence of asthenia/fatigue as compared to the placebo group ($p \leq 0.023$). Dizziness also occurred at a significantly higher incidence in the cyclobenzaprine 10-mg treatment group versus placebo treated group ($p \leq 0.023$). (See Sponsor's Table 34.)

Sponsor's Table 34 - Tabular Summary of the Most Common Adverse Events in the Double-Blind Phase III Studies (≥ 3% in Any One Treatment Group) by the Number and Percent of Participants.

	CYC 2.5 mg (N=223)		CYC 5 mg (N=464)		CYC 10 mg (N=249)		Placebo (N=469)	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants With at Least 1 Adverse Event:	98	43.9%	255	55.0%	154	61.8%	166	35.4%
Somnolence[1]	44	19.7%	135	29.1%	94	37.8%	45	9.6%
Dry Mouth[1]	31	13.9%	98	21.1%	79	31.7%	31	6.6%
Headache	16	7.2%	25	5.4%	12	4.8%	35	7.5%
Asthenia/Fatigue[2]	9	4.0%	26	5.6%	15	6.0%	12	2.6%
Nausea	9	4.0%	14	3.0%	4	1.6%	17	3.6%
Dizziness[3]	6	2.7%	13	2.8%	11	4.4%	7	1.5%

CYC=cyclobenzaprine

[1]Significantly greater incidence in the CYC 10-mg group vs any other treatment group, $p \leq 0.023$; significantly greater incidence in the CYC 5-mg group vs CYC 2.5-mg or placebo group, $p \leq 0.028$; Significantly greater incidence in the CYC 2.5-mg group vs placebo group, $p \leq 0.003$.

[2]Significantly greater incidence in the CYC 10-mg group or the CYC 5-mg group vs placebo group, $p \leq 0.024$.

[3]Significantly greater incidence in the CYC 10-mg group vs placebo group, $p \leq 0.023$.

Overall, 423 out of the 1,404 (30%) of the individuals treated with cyclobenzaprine in the 3 Phase III studies submitted in this application experienced somnolence. Sponsor's Table 35, which lists the severity rating of somnolence experienced by participants enrolled in these Phase III studies, shows that 129 out of the 932 (13.8%) participants who were treated with 5-mg of cyclobenzaprine experienced moderate to severe somnolence during the trials as compared to 156 out of 932 (16.7%) participants who rated their somnolence to be mild.

Sponsor's Table 35 - Maximum Severity of Somnolence in Phase III Studies.

Severity	CYC 2.5 mg (N=223)		CYC 5 mg (N=932)		CYC 10 mg (N=249)		Placebo (N=469)	
	n	(%)	n	(%)	n	(%)	n	(%)
Mild	30	13.4%	156	16.7%	64	25.7%	31	6.6%
Moderate	10	4.5%	105	11.3%	21	8.4%	11	2.3%
Severe	4	1.8%	24	2.6%	9	3.6%	3	0.6%

CYC=cyclobenzaprine
Note: Each participant is counted only once. If a participant had somnolence more than once, the somnolence occurrence with the worst severity rating was used to count that participant.

Of note, the sponsor reported that there was 1 auto accident involving a 49-year-old participant (AN 2058) enrolled in Protocol 008-002 randomized to 5 mg of cyclobenzaprine T.I.D., whose car's was rear ended by another vehicle. This participant did not report experiencing sedation from the study medication.

Abnormal Laboratory Tests:

Although the protocols for the 3 Phase III studies did not call for any laboratory testing or monitoring, the protocols for 8 of the remaining 10 studies did require both pre- and post-study laboratory testing of subjects. (Note: The studies which required laboratory testing as part of their protocol were: 001, 002, 003, 004, 005, 006, 007 and 012.) As shown in the following table, Sponsor's Table 36, there were 3 subjects enrolled in these 8 studies who developed laboratory adverse events. Two (2) of these subjects were treated with cyclobenzaprine, and 1 was treated with diphenhydramine.

Sponsor's Table 36 - Number and Percentage of Subjects in Each Treatment Group With at Least One Laboratory Adverse Event (AE) in the Clinical Pharmacology Studies

Treatment	Tot. No. of Subjects[1]	No. of Subjects with at Least 1 Laboratory AE	% of Subjects with at Least 1 Lab AE	No. of Subjects with Drug-Related[2] Lab AE	% of Subjects with Drug-Related[2] Lab AE
CYC	139	2	1.4%	1	0.7
DPH	43	1	2.3%	0	0
Placebo	59	0	0	0	0

CYC=cyclobenzaprine; DPH=diphenhydramine
[1]Subjects with laboratory data.
[2]Percentage of subjects with lab adverse events considered possibly, probably or definitely drug related by the investigator.

Of the 2 subjects who developed laboratory adverse events while being treated with cyclobenzaprine, only 1 was severe enough for the subject to be discontinued from

the study. (See Sponsor"s Table 37 shown below.) A 67-year-old female (Subject Number: AN0013) developed an elevated liver test (ALT) after 3 days of treatment with 5 mg of cyclobenzaprine. The study medication was discontinued but the laboratory test was still abnormal on retesting 7 days later off-drug. The investigator thought that this was possibly related to cyclobenzaprine. The other was a 40-year-old female (Subject Number: AN0008) who developed pyuria and hematuria on Day 76 of the study while off of the study medication which was cyclobenzaprine 2.5 mg. The study investigator thought that this was probably unrelated to the study medication. (Refer to Sponsor's Table 37.)

Sponsor's Table 37 - Tabular Listing of Subjects with Laboratory Adverse Events in the Clinical Pharmacology Studies

Subject No.	Age/ Gender	Treatment Group	Study Day	Total Daily Dose	Adverse Event	Drug Related
AN0013	67yo/F[1]	CYC 5.0 mg	Day 3 Day 10	5.0 mg Off Drug	ALT inc. ALT inc.	Possibly Possibly
AN0005	76yo/M	DPH 50 mg	Day 49	Off Drug	Hematuria	Def. Not
AN0008	40yo/F	CYC 2.5 mg	Day 76	Off Drug	Pyuria, Hematuria	Prob. Not

CYC=cyclobenzaprine; DPH=diphenhydramine

[1]Note: This participant was discontinued from the study due to the laboratory adverse event.

Abnormal Electrocardiogram Testing:

The protocols for Studies 001, 002, 003, 005, 007, 010 and 011 also called for pre- and post- study electrocardiogram testing (EKG). Although there were no appreciable changes in mean QT interval after treatment with cyclobenzaprine, there was 1 patient enrolled in Study 005-001 who developed an abnormal post-study EKG following treatment with 3 different doses (2.5 mg, 5 mg and 10 mg) of cyclobenzaprine. This 40-year-old female (AN 0008) was found to have premature ventricular contractions on EKG. She also reported having palpitations and anxiety which subsequently resolved. The study investigator thought that the EKG changes were possibly related to the study medication.

Clinical (Blood Pressure and Pulse) Safety Measurements:

Blood pressure and pulse data collected from the 2 double-blind studies, Studies 006 and 008, were analyzed for any clinically meaningful changes. There was only 1 report of tachycardia which occurred in a participant from the placebo group and no reports of blood pressure increases. The following 2 tables, Sponsor's Tables 38 and 39, list the changes in sitting systolic and diastolic blood pressures and sitting pulses

measured at the entry and exit visits for these 2 studies. Although participants treated with cyclobenzaprine did have some lowering of both their systolic and diastolic blood pressures, these changes were comparable to those experienced by participants in the placebo group. (See Sponsor's Table 38 shown below.)

Sponsor's Table 38 - Mean Changes in Sitting Systolic and Diastolic Blood Pressure (mm hg) in Studies 006 and 008.

Measurement	Treatment	No.	Baseline		Final Visit		Change	
			Mean	SD	Mean	SD	Mean	SD
Study 006								
Systolic BP	**CYC 10 mg**	240	125.1	15.0	122.8	14.1	-2.3	10.6
	CYC 5 mg	236	122.7	15.5	120.8	13.9	-1.9	11.5
	Placebo	243	123.4	15.3	123.2	16.4	-0.2	11.7
Diastolic BP	**CYC 10 mg**	240	79.2	9.4	78.3	8.8	-0.9	7.4
	CYC 5 mg	236	77.8	8.7	77.4	8.6	-0.4	8.2
	Placebo	243	78.2	9.8	77.2	9.8	-1.0	8.2
Study 008								
Systolic BP	**CYC 5 mg**	217	122.7	16.6	121.6	15.9	-1.1	10.5
	CYC 2.5 mg	217	123.6	15.9	122.6	14.7	-1.0	11.9
	Placebo	212	122.3	16.6	121.7	16.0	-0.7	12.5
Diastolic BP	**CYC 5 mg**	217	78.0	10.0	77.5	10.1	-0.4	8.6
	CYC 2.5 mg	217	78.3	8.9	78.1	8.7	-0.3	7.8
	Placebo	212	78.0	9.9	76.3	9.9	-1.7	8.1

In terms of cyclobenzaprine's effect on pulse rate, participants treated with cyclobenzaprine in Studies 006 and 008, experienced a slight increase in pulse rate as compared to the placebo treated patients. (Refer to Sponsor's Table 39 Shown below.)

Sponsor's Table 39 - Tabular Listing of Mean Changes in Sitting Pulse

(Beats/Min) in Protocols 006 and 008.

Treatment	No.	Baseline		Final Visit		Change	
		Mean	SD	Mean	SD	Mean	SD
Study 006							
Cyclobenzaprine 10 mg	236	73.7	9.3	78.0	10.2	4.3	10.3
Cyclobenzaprine 5 mg	235	74.0	8.9	77.1	9.1	3.0	8.9
Placebo	242	74.3	8.6	74.5	8.6	0.2	8.4
Study 008							
Cyclobenzaprine 5 mg	216	74.1	9.0	77.1	9.9	3.0	9.5
Cyclobenzaprine 2.5 mg	216	74.0	8.9	77.7	9.6	3.6	8.7
Placebo	211	73.1	10.3	73.4	9.4	0.3	8.7

Both the changes in blood pressure and pulse experienced by participants in these studies are clinically insignificant.

Drug-Demographic Interactions:

As part of the safety analysis for this application, the sponsor looked at the occurrence of adverse events in participants enrolled in the 3 Phase III studies by the following demographic parameters: gender, age and race. As demonstrated in the data generated from the Phase III studies listed in the following table, Sponsor's Table 40, no gender-related differences are noted in terms of adverse events experienced by the male and female populations treated with cyclobenzaprine in this application.

Sponsor's Table 40 - Adverse Events (AEs) with Incidences ≥ 3% Listed by Body

System and Gender in the Phase III Studies by Number (%) of Participants (Pts.)

Adverse Event by Body System	Cyclobenzaprine		Placebo	
	Males (n=617)	Females (n=787	Males (n=200)	Females (n=269)
No. of Pts. with ≥ any AE:	336(54.5)	441(56.0)	60(30.0)	106(39.4)
Pts. without AEs:	281(45.5)	346(44.0)	140(70.0)	163(60.6)
Body as a Whole/Site Unspecific: Asthenia/Fatigue:	54 (8.8) 34 (5.5)	62 (7.9) 44 (5.6)	6 (3.0) 3 (1.5)	17 (6.3) 9 (3.3)
Cardiovascular System:[1]	1 (0.2)	3 (0.4)	1 (0.5)	1 (0.4)
Digestive System: Dry Mouth:	153(24.8) 113(18.3)	190(24.1) 149(18.9)	29 (14.5) 15 (7.5)	40(14.9) 16(5.9)
Metabolic/Nutritional/Immune System:[1]	1 (0.2)	2 (0.3)	1 (0.5)	0
Musculoskeletal System:[1]	20 (3.2)	17 (2.2)	3 (1.5)	10 (3.7)
Nervous System/Psychiatric: Dizziness: Headache: Somnolence:	228 (37.0) 22 (3.6) 45 (7.3) 189(30.6)	315(40.0) 26 (3.3) 70 (8.9) 234(29.7)	26(13.0) 1 (0.5) 7 (3.5) 14 (7.0)	64(23.8) 6 (2.2) 28(10.4) 31(11.5)
Respiratory System:[1]	29 (4.7)	37 (4.7)	8 (4.0)	12 (4.5)
Skin and Skin Appendage:[1]	8 (1.3)	11 (1.4)	3 (1.5)	3 (1.1)
Special Senses:[1]	8 (1.3)	28 (3.6)	2 (1.0)	4 (1.5)
Urogenital System:[1]	6 (1.0)	8 (1.0)	0	4 (1.5)

Note: This table is based on counts of participants. Although a participant may have had 2 or more AEs, the person is counted only once in the body system total and in "Number (%) of participants with any AE."
[1]All individual AEs categorized in this body system have an incidence <3% in males and females who received cyclobenzaprine.

Sponsor's Table 41 lists adverse event data generated from the Phase III studies by participants <65 years of age versus ≥65 years of age. In this table there appears to be age-related differences in the incidences of many of the adverse events such as body as a whole (8.5% vs 4.1%, asthenia/fatigue: 5.9% vs 0%), the digestive system (24.0% vs 32.4%, dry mouth: 18.3% vs 24.3%), nervous system/psychiatric (38.9% vs 33.8%, dizziness: 3.5% vs 1.4% and headache: 8.3% vs 5.4%), respiratory system (4.9% vs 1.4%), special senses (2.5% vs 4.1%), and the urogenital system (0.9% vs 2.7%). Due to the small number of individuals ≥65 exposed to cyclobenzaprine (n=74) in the Phase III studies, no valid conclusions can be drawn from this data base regarding the possibility of age-related adverse events associated with the use of cyclobenzaprine.

Sponsor's Table 41 - Adverse Events (AEs) with Incidences ≥ 3% Listed by Body System and Age (<65, ≥65) in the Phase III Studies by Number (%) of Participants (Pts.)

Adverse Event by Body System	Cyclobenzaprine		Placebo	
	<65 (n=1330)	≥65 (n=74)	<65 (n=439)	≥65 (n=30)
No. of Pts. with > any AE:	738(55.5)	39 (52.7)	161 (36.7)	5 (16.7)
Pts. without AEs:	592(44.5)	35 (47.3)	278 (63.3)	25(83.3)
Body as a Whole/Site Unspecific: Asthenia/Fatigue:	113 (8.5) 78 (5.9)	3 (4.1) 0	22 (5.0) 12 (2.7)	1 (3.3) 0
Cardiovascular System:[1]	4 (0.3)	0	2 (0.5)	0
Digestive System: Constipation Dry Mouth:	319 (24.0) 16 (1.2) 244 (18.3)	24 (32.4) 3 (4.1) 18 (24.3)	66(15.0) 7 (1.6) 29(6.6)	3(10.0) 0 2(6.7)
Metabolic/Nutritional/Immune System:[1]	3 (0.2)	0	1 (0.2)	0
Musculoskeletal System:[1]	35 (2.6)	2 (2.7)	13 (3.0)	0
Nervous System/Psychiatric: Dizziness: Headache: Somnolence:	518(38.9) 47(3.5) 111(8.3) 401(30.2)	25 (33.8) 1 (1.4) 4 (5.4) 22 (29.7)	87(19.8) 7(1.6) 35(8.0) 43(9.8)	3 (10.0) 0 0 2 (6.7)
Respiratory System:[1]	65 (4.9)	1 (1.4)	20 (4.6)	0
Skin and Skin Appendage:[1]	18 (1.4)	1 (1.4)	6 (1.4)	0
Special Senses:[1]	33 (2.5)	3 (4.1)	6 (1.4)	0
Urogenital System:[1]	12 (0.9)	2 (2.7)	4 (0.9)	0

Note: This table is based on counts of participants. Although a participant may have had 2 or more AEs, the person is counted only once in the body system total and in "Number (%) of participants with any AE."
[1]All individual AEs categorized in this body system have an incidence <3% in males and females who received cyclobenzaprine.

Analysis of adverse event data from the Phase III studies was also analyzed for any racial differences. Since so few minoritories other than black participants were enrolled in these studies, the sponsor limited its racial adverse event analysis to caucasians and blacks. As shown in Sponsor's Table 42, black participants overall had a lower incidence of adverse events associated with treatment with both cyclobenzaprine (35/109; 32.1%) and placebo (11/43; 25.6%) as compared to caucasian participants (707/1247; 56.7%, and 148/411; 36.0%, respectively). This trend continues for all of the body system listed in Sponsor's Table 42 with the exception of the urogenital system where blacks reported more adverse events (2/109; 1.8%) associated with cyclobenzaprine treatment than caucasians (11/1247; 0.9%).

Again no valid conclusions can be drawn from this data base regarding the possibility of race-related adverse events associated with the use of cyclobenzaprine due to the relatively small number of black participants who were enrolled in the Phase III studies. (Refer to Sponsor's Table 42.)

Sponsor's Table 42 - Adverse Events (AEs) with Incidences ≥ 3% Listed by Body System and Race (Caucasian, Black) in the Phase III Studies by Number (%) of Participants (Pts.)

Adverse Event by Body System	Cyclobenzaprine		Placebo	
	Caucasian (n=1247)	Black (n=109)	Caucasian (n=411)	Black (n=109)
No. of Pts. with > any AE:	707 (56.7)	35(32.1)	148(36.0)	11(25.6)
Pts. without AEs:	540 (43.3)	74(67.9)	263(64.0)	32(74.4)
Body as a Whole/Site Unspecific: Asthenia/Fatigue:	106 (8.5) 72 (5.8)	7(6.4) 4(3.7)	19 (4.6) 10 (2.4)	3 (7.0) 2 (4.7)
Cardiovascular System:[1]	4 (0.3)	0	2 (0.5)	0
Digestive System: Dry Mouth:	304 (24.4) 233 (18.7)	18(16.5) 15(13.8)	62(15.1) 28(6.8)	3 (7.0) 2 (4.7)
Metabolic/Nutritional/Immune System:[1]	3 (0.2)	0	1 (0.2)	0
Musculoskeletal System:[1] Pain, Back	31 (2.5) 5 (0.4)	6(5.5) 4(3.7)	12 (2.9) 2 (0.5)	0 0
Nervous System/Psychiatric: Dizziness: Headache: Somnolence:	492 (39.5) 40 (3.2) 103 (8.3) 384 (30.8)	27(24.8) 5(4.6) 8(7.3) 21(19.3)	83 (20.2) 7 (1.7) 33 (8.0) 42 (10.2)	4 (9.3) 0 1 (2.3) 2 (4.7)
Respiratory System:[1]	61 (4.9)	1(0.9)	19 (4.6)	1 (2.3)
Skin and Skin Appendage:[1]	19 (1.5)	0	5 (1.2)	0
Special Senses:[1]	35 (2.8)	1(0.9)	5 (1.2)	0
Urogenital System:[1]	11 (0.9)	2(1.8)	2 (0.5)	2 (4.7)

Note: This table is based on counts of participants. Although a participant may have had 2 or more AEs, the person is counted only once in the body system total and in "Number (%) of participants with any AE."

[1]All individual AEs categorized in this body system have an incidence <3% in males and females who received cyclobenzaprine.

Drug-Disease Interactions:

Overall the participants enrolled in the clinical studies for this NDA were generally healthy. The incidence of concomitant diseases was relatively low for those enrolled in the Phase III studies, where this information was specifically collected. Some of the more commonly reported background medical disorders were hypertension (12%), arthritis (4%), hypercholesterolemia (3%), and diabetes mellitus (2%). Only 1 report of worsening concomitant disease was noted in an individual, treated with cyclobenzaprine, who developed an increased blood pressure.

The sponsor found 2 patients in the data base with histories of hyperthyroidism and 22 patients with histories of hypothyroidism who were treated with cyclobenzaprine during the Phase III studies. Although these patients did not report any endocrine adverse events it is not clear from the information submitted by the sponsor if they had experienced any arrhythmias associated with the use of the drug.

Drug-Drug Interactions:

In support of this submission, the sponsor did not conduct any drug-drug interaction studies. Cyclobenzaprine, is structurally related to the tricyclic class of drugs, is mentioned in a warning statement regarding the increased risk for seizures for the analgesic drug, tramadol (Ultram), in patients who take these drugs concomitantly. The sponsor examined the safety data base for any drug-drug interactions associated with the concomitant use of cyclobenzaprine and other analgesics such as ibuprofen, acetaminophen and aspirin during the Phase III studies. With the exception of headache, the incidence of adverse events were similar to that of the population who did not use analgesics during the trials. (Note: Although 9% of all patients who received cyclobenzaprine in the Phase III studies reported having headaches, 52% of those who took acetaminophen and 33% of those who took ibuprofen while enrolled reported having a headache. The sponsor has suggested that this finding may be an artifact since individuals suffering from headaches are more likely to use analgesics to relieve their pain.) Of note individuals taking other drugs known to cause pharmacodynamic interactions with cyclobenzaprine were prohibited from entering (i.e., Study Protocol 009). Thus, limited information can be gained regarding the potential for drug-drug interactions from a post-hoc analysis of the reported adverse drug events contained in this safety data base.

Withdrawal Phenomena/Abuse Potential:

There were no reports of withdrawal effects in any of the patients who participated in the short-term studies submitted in support of this NDA. (Note: These safety issues are discussed in greater detail by Dr. Michael Klein in his review of cyclobenzaprine's potential for abuse.)

Reviewer's Comment's:

1. Review of the safety data base for these 13 short term studies does not reveal any new potential drug side effects associated with the use of cyclobenzaprine. The information generated from these studies is consistent with what is already known about cyclobenzaprine's safety profile.

2. Although cyclobenzaprine is known to cause arrhythmias, the 1 case report of death due to an myocardial infarction contained in this submission was confounded by the patient's concomitant use of cocaine and her underlying risk factors for heart disease.

3. Of the remaining 4 serious adverse events which occurred in patients enrolled in the clinical studies contained in this submission, none appear to be related to the use of cyclobenzaprine with the exception of the patient who was hospitalized with worsening back pain after taking cyclobenzaprine 2.5 mg T.I.D. for 2 days. This later case was probably the result of a therapeutic failure due to the low dose of cyclobenzaprine that the patient was taking.

4. The most frequently reported adverse event in this safety data base was somnolence followed by dry mouth which is consistent with the drug's known safety profile. (See Sponsor's Table 33.)

5. With the exception of nausea, the occurrence of somnolence, dry mouth, headache, asthenia/fatigue, and dizziness appears to be dose-dependent in this submission. (Refer to Sponsor's Table 34.)

6. Although the abnormal laboratory changes reported in the clinical safety data base were insignificant, no conclusions regarding the potential for laboratory abnormalities can be drawn. This is because the data presented for review in this submission contained data from subjects enrolled in the short-term PK/PD studies, and not in longer double-blind placebo-controlled studies. (See Sponsor's Tables 35, 36 and 37.)

7. Cyclobenzaprine is known to cause cardiac arrhythmias. EKG monitoring was performed in 7 out of the 13 study protocols, for PK/PD or psychomotor information. Only one abnormal EKG with premature ventricular contractions was found in a 40-year-old female patient who also complained of having palpitations and anxiety. No EKG monitoring was done in the 2 double-blind, placebo controlled efficacy studies or in the actual use study. Thus, the population monitored may not accurately reflect the risk for the development of arrhythmias associated with the use of this product.

8. Although patients in the 2 double-blind, placebo controlled studies treated with cyclobenzaprine did experience some lowering of their sitting systolic and diastolic blood pressures, monitored changes in their mean pulse rate were minimal. This is consistent with what is already known about cyclobenzaprine's ability to lower blood pressure. Due to the limited number of elderly patients enrolled in these studies, no

valid conclusions can be drawn regarding the potential for the development of symptomatic hypotension in this population, who may also be at risk for falling. (See Sponsor's Tables 39, 40 and 28.)

9. No valid conclusions can be made regarding the sponsor's post-hoc drug-demographic interactions for the age and race subgroup adverse event analyses in view of the relatively low numbers of elderly patients ≥ 65 years of age, and ethnic minorities who participated in these studies. (Refer to Sponsor's Tables 41 and 42.)

10. With the exception of patients with hepatic impairment, the sponsor did not specifically study patients with underlying medical disorders such as glaucoma, thyroid disease, heart disease, prostatic hypertrophy, or seizures. Thus, the sponsor's post-hoc drug-disease analysis in which they looked for reports of worsening of the underlying medical condition provides little information about the potential for adverse events to occur in consumers with underlying medical diseases.

11. The sponsor did not perform any drug-drug interaction studies in this submission despite reports of the increase risk for various serious (i.e, seizures) and lethal adverse events (i.e., hyperpyretic crisis,) that have been reported to have occurred in patients who have taken prescription strength doses of cyclobenzaprine with other drugs such as tramadol, monoamine oxidase inhibitors, alcohol, barbiturates, and sedatives.

Conclusion: Although the data generated from the 13 clinical studies in this safety data base is consistent and supportive of what is known regarding cyclobenzaprine's safety profile, specific information regarding its adverse event profile in the elderly ≥65 years of age, and ethnic minorities is lacking. In addition, the sponsor did not submit any clinical trial data regarding specific drug-drug and drug-disease interactions which could be potentially hazardous in consumers using this product OTC.

III - Safety Data Generated From Postmarketing Experience and Literature Reports Associated with Prescription Strength Cyclobenzaprine.

Since cyclobenzaprine's introduction in 1977 to the U.S. prescription market, the sponsor estimates that more than 90,000,000 prescriptions have been written for Flexeril® and that more than 1,500,000,000 tablets have been dispensed by Merck. Due to the recurrent nature of muscle spasm, it is impossible to estimate patient exposure for the product since multiple prescriptions may have been given to the same patients over time. In support of this prescription to OTC switch application for cyclobenzaprine, the sponsor has submitted the additional following safety information for review:

1. The results of postmarketing surveillance studies that were part of the 1977 approval action for cyclobenzaprine 10 mg.

2. Spontaneous reports to the manufacturer arising from the drug's marketed use.

3. The results of a literature search from 1965 to June 1, 1998 which identified information regarding the safety and efficacy of cyclobenzaprine.

4. Overdose data from the American Association of Poison Control Centers' (AAPCC) Toxic Exposure Surveillance System (TESS).

The first 3 pieces of information will be discussed below. The overdose information from the AAPCC's TESS data base has been reviewed by Dr. Michael Klein. Abstracts of the 126 publications generated in the sponsor's literature search can be found in Appendix III at the end of this review.

Postmarketing Studies:

The sponsor conducted a postmarketing surveillance study and a comparative survey as part of the marketing agreement reached with the agency in 1977. The results of both of these trials were previously submitted and reviewed by the agency. Thus the following discussion of the studies' results will be limited to highlights of their safety data. The postmarketing study was a multicenter (1,991 physicians), open-label study which involved 6,311 patients treated with 10 mg T.I.D. of cyclobenzaprine for 14 days in 1977. During this study, the patients were allowed to titrate the dose of cyclobenzaprine as needed. The comparative survey was another multicenter (685 physicians), open-label, short-term study which evaluated 1,296 patients with acute muscle spasm who were treated with either cyclobenzaprine 10 mg or with other muscle relaxants conducted in 1978. Both of these studies were designed to capture information regarding the occurrence of adverse events, in particular any episodes of confusion, tachycardia, disorientation, hallucinations, arrhythmias, or seizures associated with the use of cyclobenzaprine. The overall adverse event profiles for the

populations enrolled in these 2 studies was similar to that demonstrated in the preceding clinical safety review for the OTC switch application. The following table, Sponsor's Table 43, lists the incidences of the targeted 6 adverse events specifically looked for in these studies, as well as some of the other commonly associated adverse events associated with cyclobenzaprine.

Sponsor's Table 43 - Adverse Events (AE) in the Cyclobenzaprine 10-mg Surveillance and Comparative Studies by the Number (%) of Patients

Adverse Event	Surveillance Study	Comparative Survey	Total
	N=6,311	N=1,296	N=7,607
Arrhythmia	5 (0.1%)	2 (0.2%)	7 (0.1%)
Asthenia	67 (1.1%)	9 (0.7%)	76 (1.0%)
Confusion	88 (1.4%)	18 (1.4%)	106 (1.4%)
Disorientation	52 (0.8%)	10 (0.8%)	62 (0.9%)
Dizziness	208 (3.3%)	43 (3.3%)	251 (3.3%)
Dry Mucous Membranes	445 (7.1%)	64 (4.9%)	509 (6.7%)
Fatigue/Tiredness	13 (0.2%)	2 (0.2%)	15 (0.2%)
Hallucination	99 (1.6%)	15 (1.2%)	114 (1.5%)
Seizure	1 (-)	0	1 (-)
Somnolence	1023(16.2%)	216(16.6%)	1238(16.3%)
Tachycardia	53 (0.8%)	12 (0.9%)	65 (0.9%)

Confusion (62/7607; 1.4%), disorientation (62/7607; 0.9%), and tachycardia (65/7,607; 0.9%) were the 3 most commonly reported of the specifically sought after adverse events in these 2 studies. The occurrences of somnolence (1238/7607; 16.3%), dry mucous membranes (509/7607; 6.7%), and dizziness (251/7607; 3.3%) were comparable to what was seen in the clinical trial safety data base.

Spontaneous Reports to the Manufacturer Arising From the Drug's Marketed Use:

As of August 12, 1998 the sponsor's Worldwide Averse Experience System (WAES) database contained a total of 968 adverse event reports associated with the use of cyclobenzaprine. Sixty-six (66) of the 968 adverse event reports in the WAES data base were cases of drug overdoses with cyclobenzaprine. Sponsor's Table 44 shown below, lists by body system the 902 spontaneous adverse event reports and the 186 case reports which met regulatory criteria for classification as serious in nature.

Sponsor's Table 44 - Number of Patients with Adverse Events and Serious Adverse Events by Body System Received as Spontaneous Reports During Marketed Use Excluding Overdose Cases

Body System	No. of Pts. with an AE	No. of Pts. with a Serious AE
Body as a Whole/Site Unspecific	274	55
Cardiovascular System	124	40
Digestive System	133	20
Endocrine System	15	4
Eyes, Ears, Nose Throat	67	8
Hemic and Lymphatic System	35	11
Hepatobilary System	45	22
Immune System	37	3
Metabolism and Nutrition	36	5
Musculoskeletal System	36	15
Nervous System	223	42
Psychiatric Disorder	237	49
Respiratory System	34	14
Skin and Skin Appendages	88	11
Urogenital System	92	21
Total:	902	186

Note: The same patient may appear in more than one body system.

Only 475 of the 902 spontaneous adverse event reports collected by the sponsor listed the individual's age, out of which 89 (19%) were reports of adverse events that had occurred in elderly ≥ 65 years of age. Based on estimates by the sponsor approximately 14% of the prescriptions written for cyclobenzaprine were for patients ≥ 65 years of age which means that this segment of the population has a slightly greater proportion of spontaneous adverse event reports than other age groups.

The frequently reported adverse events were mental disorder (122 case reports), hallucination (80 case reports), rash (39 case reports), somnolence (37 case reports), nausea (37 case reports), dizziness (34 case reports), confusion (27 case reports), and seizures (26 case reports) are shown in Sponsor's Table 45.

Sponsor's Table 45 - WAES Spontaneous Adverse Event Reports with ≥ 9 Reports Listed by Body System

Total Reports	Number
	902
Body as a Whole/Site Unspecified	**274**
Abdominal Pain	10
Asthenia/Fatigue	22
Chest Pain	15
Condition Unspecified	18
Concurrent Condition	25
Dizziness	34
Drug Interaction	21
Dry Mucous Membranes	32
Edema	13
Fever	11
Lack of Response	13
Product Misuse	10
Syncope	16
Worsening Pre-existing Condition	9
Cardiovascular System:	**124**
Arrhythmia	9
Cardia Arrest	9
Hypotension	13
Palpitation	11
Tachycardia	33
Digestive System	**133**
Constipation	10
Diarrhea	11
Dry Mouth	16
Dyspepsia	9
Nausea	37
Vomiting	18
Eyes, Ears, Nose, Throat	**67**
Blurred Vision	12
Tinnitus	14
Visual Disturbance	12
Hepatobilary System	**45**
Hepatic Function Abnormality	20
Hepatitis	13
Jaundice	9

Note: Although a participant may have had 2 or more adverse events, the participant is counted only once within a body system category. The same participant may appear in different categories.

Sponsor's Table 45 (Cont.) - WAES Spontaneous Adverse Event Reports with ≥ 9 Reports Listed by Body System

Immune System	**37**
Allergy	12
Drug Allergy	10
Hypersensitivity Reaction	13
Nervous System	**223**
Dysarthria	9
Headache	22
Insomnia	15
Muscular Spasm	14
Paresthesia	16
Seizure/Grand Mal Seizure	26
Somnolence	37
Tremor	14
Psychiatric Disorder	**237**
Agitation	10
Confusion	27
Depression	20
Disorientation	23
Drug Withdrawal Disorder	9
Hallucination	80
Memory Impairment	12
Mental Acuity Decreased	12
Mental Disorder	122
Psychosis	23
Respiratory System	**34**
Dyspnea	14
Skin and Skin Appendages	**88**
Alopecia	12
Pruritus	14
Rash	39
Urticaria	13
Urogenital System	**92**
Product Use During Pregnancy	15
Urinary Retention	24

Note: Although a participant may have had 2 or more adverse events, the participant is counted only once within a body system category. The same participant may appear in different categories.

The following discussion of the postmarketing adverse event case reports will concentrate on reported deaths and reports that were either classified as serious in nature or that signaled high for the body system listed.

Death Reports:

Fifty-one (51) out of the 968 adverse event reports in the WAES database were

reports of death in individuals who had taken cyclobenzaprine. Five (5) of these 51 death reports were cases of fetal exposure to cyclobenzaprine during pregnancy. These will be discussed separately later in this review. Of the remaining 46 case reports, 12 described cases of either accidental or intentional overdoses with cyclobenzaprine. (Note: These are discussed by Dr. Michael Klein in the drug abuse review of this application.) Sponsor's Table 46 lists and summarizes the 34 remaining death reports. Eight out of the 34 deaths occurred in elderly ≥ 65 years of age. Only 1 of the 3 fatalities due to liver failure may be secondary to drug-induced hepatitis from long term use of cyclobenzaprine (Case Number 83050011). There were also 3 case reports of suicides which are probably unrelated to the drug. There were 11 fatalities where individuals died from cardiac events, 9 cases of which were sudden deaths. Many of these individuals had prior histories of cardiac disease. (Refer to Sponsor's Table 46.)

Sponsor's Table 46 - WAES Reports with Fatal Outcomes Excluding Overdoses and In Utero Exposure

WAES No.	Age/ Gender	Synopsis
78040005	79yo/F	Hypertensive diabetic treated with cyclobenzaprine for 6 days. Hospitalized S/P fractured humerus due to night-time fall. Developed respiratory failure, shock and died. Death attributed to coronary insufficiency.
78050045	55yo/M	S/P knee surgery took cyclobenzaprine and propoxyphene for 2 days. Died due to self-inflicted gunshot wound (suicide).
79010036	70yo/F	H/O diabetes, breast cancer, and hypothyroidism. Hospitalized due to urinary retention, constipation, confusion S/P 2-days of treatment with cyclobenzaprine and sulindac. Condition improved. Died due to cardiac arrest.
79020005	36yo/F	H/O rheumatoid arthritis treated with prednisone, naproxen, bethanechol, and cyclobenzaprine for 4 months. Died due to hepatitis.
81100121	Unk/F	On chemotherapy developed pancytopenia following treatment with cyclobenzaprine. Died due to cerebral hemorrhage.
82020086	70yo/M	H/O back pain treated with sulindac and cyclobenzaprine 60 mg/day. Developed confusion and was hospitalized. Died due to pulmonary embolism.
82030164	44yo/M	H/O rheumatic fever, hypertension, syncope. S/P treatment with cyclobenzaprine, acetaminophen, codeine for 5-days suddenly died. Died due to myocardial hypertrophy.
82090216	Unk/Unk	Physician reported hearing about 7 deaths due to cyclobenzaprine. No further information given.
82120185	56yo/M	H/O hypertension treated with diuretic therapy. Developed flu-like illness with back pain. Treated with cyclobenzaprine for 1 day and died. Death was attributed to respiratory failure.

Sponsor's Table 46 (Cont.) - WAES Reports with Fatal Outcomes Excluding Overdoses and In Utero Exposure

WAES No.	Age/ Gender	Synopsis
83010011	76yo/M	H/O Hypertension, obesity and back pain treated with other muscle relaxants. Sudden death due to myocardial infarction on day he started cyclobenzaprine.
83050011	67yo/F	H/O Alzheimer's Disease and myoclonic seizures. Treated with cyclobenzaprine. Died due to hepatitis. Hepatitis BsAg positive. Liver biopsy consistent with either a viral hepatitis or toxic drug effect.
83070005	29yo/M	Patient had been given prescriptions for cyclobenzaprine and corticosteroid. Death due to self-inflicted gunshot wound (suicide). At autopsy, cyclobenzaprine levels were undetectable.
83120155	41yo/F	Treated with cyclobenzaprine S/P auto accident and developed dermatomyositis. Died 4 months later.
84010216	Unk/Unk	Died while being treated for injuries received in a fall with cyclobenzaprine.
84110239	63yo/M	Hospitalized for evaluation of chest pains treated with cyclobenzaprine, sulindac, cimetidine with H/O peptic ulcer. Died due to GI bleed with hepatic failure.
86050182	36yo/M	H/O Multiple blood transfusions. Hospitalized for evaluation of hallucinations after taking cyclobenzaprine for 2 days. Aspirated. Died due to hepatic failure.
86090135	61yo/F	H/O Rheumatoid arthritis and coronary artery disease treated with multiple meds including cyclobenzaprine $\geq$ 1 year. Developed acute shortness of breath and died. Death was attributed to imipramine toxicity.
86090373	20yo/M	Developed muscle cramps S/P football practice. Treated with cyclobenzaprine and hydroxyzine. Died while being transported to a hospital. Autopsy revealed rhabdomyolysis, sickle cell trait; and acute hemolytic anemia.
87040324	32yo/F	Hospitalized for depression and chronic pain treated with cyclobenzaprine, codeine, and barbiturates. Developed fever, rhabdomyolysis and suffered a cardiac arrest S/P 1-days treatment with doxepin and chlorpromazine. Died 29 days later due to hyperpyrexia.
87060484	Unk/M	Drank alcohol while taking cyclobenzaprine and died in a bar fight.
88050101	20yo/F	H/o Fibrositis treated with cyclobenzaprine. Died of unknown causes.
88060670	Unk/M	H/O coronary artery disease. Died a sudden death after leaving ER S/P treatment with cyclobenzaprine for pain in the neck and upper extremity.
89030734	39yo/M	Died due to cerebral edema and hyperthermia after taking cyclobenzaprine, terfenadine, and monoamine oxidase inhibitors.
89090773	Unk/F	Suicide death. Method not reported.

Sponsor's Table 46 (Cont.) - WAES Reports with Fatal Outcomes Excluding Overdoses and In Utero Exposure

WAES No.	Age/ Gender	Synopsis
90040005	61yo/F	H/O Rheumatic heart disease, S/P mitral valve replacement. Treated with cyclobenzaprine. Hospitalized and died due congestive heart failure 1 month later.
91010551	62yo/M	H/O Back pain treated with cyclobenzaprine. Died due to a ruptured cerebral aneurysm.
91110797	Unk/Unk	H/O Alcoholism. Died due to hyperthermia S/P treatment with cyclobenzaprine and mono-amine oxidase inhibitor.
92030852	23yo/M	H/O Back pain treated with cyclobenzaprine, acetaminophen, hydrocodone, and methocarbamol. Developed thrombocytopenia and died due to subdural hematoma.
93030012	60yo/M	H/O Thyroid cancer and osteoarthritis treated with cyclobenzaprine, hydrocodone, and naproxen. Developed orthopnea. Died due to sudden death that was attributed to myocarditis.
95050307	Unk/F	Death due to hypothermia after loosing consciousness outside. Toxicology tests showed measurable levels of cyclobenzaprine, zolpidem, propoxyphene, and doxepin.
95071757	82yo/M	Nursing home resident who developed hallucinations after treatment with cyclobenzaprine. Died of chronic obstructive pulmonary disease.
95121405	Unk/Unk	Died due to respiratory failure S/P taking cyclobenzaprine with unspecified central nervous system depressants.
96081899	73yo/M	Treated with cyclobenzaprine for back pain during hospitalization for pneumonia. Died due to pneumonia.
97091249	74yo/M	H/O Diabetes, heart disease, ventilator-dependent pulmonary disease. Died due to neuroleptic malignant syndrome S/P treatment with cyclobenzaprine, metoclopramide, neuronin, and multiple other medications.

Unk=unknown

Body as a Whole:

The most frequently reported adverse events for body as a whole were: dizziness (34 reports), dry mucus membranes (32 reports) and asthenia/fatigue (22 reports). This is consistent with what was seen in the safety data base generated from the clinical trials previously discussed. In addition there were 23 case reports of drug-drug interactions. (Refer to Sponsor's Table 47 shown below). Three (3) of these cases involved patients who died and are discussed above. Eight (8) case reports involved the use of alcohol, 4 reports involved the use of monoamine oxidase (MAO) inhibitors, and 3 reports were with fluoxetine (an SSRI) associated with the use of cyclobenzaprine. These are all drug-drug combinations that are known to cause

interactions and are reflected in the current prescription labeling of the 10-mg dose of cyclobenzaprine. The remaining 9 cases involved a mixture of agents from a variety of drug classes. Thus, no definitive conclusions can drawn.

Sponsor's Table 47 - Review of Postmarketing Drug Interaction Adverse Events

WAES No.	Age/Gender	Concomitant Drug	Adverse Event
78060061	Unk/F	Alcohol	Rash.
78070063	Unk/Unk	Alcohol	Report of 2 individuals with hallucinations, disorientation, and confusion.
81060092	40yo/F	Alcohol	Psychosis with visual hallucinations.
82100189	39yo/F	Zomepirac	Hypersensitivity reaction with dyspnea, hypotension, urticaria.
87060484*	Unk/M	Alcohol	Trauma (bar fight).
89030734*	39yo/M	Terfenadine and tranylcypromine	Cerebral edema and hyperthermia.
89030912	40yo/M	Tranylcypromine and codeine	Fever and myoclonus.
91061475	61yo/F	Fluoxetine, lisinopril, phenytoin and ranitidine	Neurological disorder.
91110797*	Unk/Unk	Tranylcypromine	Hyperthermia.
92030649	40yo/F	Fluoxetine, hydrocodone and acetaminophen	Hallucinations, disorientation and tachycardia.
93010811	Unk/F	Oral contraceptive	Pregnancy (ineffective oral contraception).
93051371	Unk/M	Alcohol	Elevated blood alcohol level.
94051292	37yo/F	Nifedipine, doxepin, zolpidem, cimetidine and dicyclomine.	Elevated blood pressure, grogginess, and dizziness.
94060069	49yo/M	Lovastatin, oxycodone, naproxen, acetaminophen, glyburide, chlorpheniramine	Rhabdomyolysis.
94081514*	27yo/M	Alcohol, cocaine, ranitidine	Pulmonary hemorrhage with edema
94120189	Unk/Unk	Nadolol	Recurrence of back spasms.
95081896	20yo/F	Antibiotics	Rash.
95081896	33yo/F	Amitriptyline, alcohol and indomethacin	Trauma due to disorientation.
96022201	41yo/M	Alcohol and hydrocodone	Hyperreflexia and myoclonus with elevated serum calcium

*Outcome was death; Unk=unknown

Sponsor's Table 47 (Cont.)- Review of Postmarketing Drug Interaction Adverse Events

WAES No.	Age/Gender	Concomitant Drug	Adverse Event
95111970	Unk/Unk	Monoamine oxidase inhibitor	Not specified.
96102303	59yo/F	Droperidol, fluoxetine, diclofenac, and simvastatin	Prolonged QT interval and ventricular fibrillation.
97020275	Unk/Unk	Warfarin and glyburide	Increased prothrombin time.
97102255	Unk/M	Propoxyphene, antibiotics, acetaminophen, and cough medicine	Hallucinations, psychosis, and depression.

* Outcome was death; Unk=unknown

Cardiovascular System:

As noted in the above table, Sponsor's Table 45, the 3 most commonly reported adverse events for the cardiovascular system were: tachycardia (33 reports), hypotension (13), and palpation (11). Cyclobenzaprine, structurally similar to the tricyclic antidepressants which are known to cause cardiac arrhythmias, was also associated with 9 case reports of arrhythmia and 13 cases of cardiac arrest, 8 of which were fatal.

Sponsor's Table 48 - WAES Reports of Cardiac Arrest, Ventricular Fibrillation, or Ventricular Tachycardia with Prescription Cyclobenzaprine

Fatal Outcome:		
82030164	44yo/M	H/O rheumatic fever, hypertension, syncope. S/P treatment with cyclobenzaprine, acetaminophen, codeine for 5-days suddenly died. Died due to myocardial hypertrophy.
82120185	56yo/M	H/O hypertension treated with diuretic therapy. Developed flu-like illness with back pain. Treated with cyclobenzaprine for 1 day and died. Death was attributed to respiratory failure.
83010011	76yo/M	H/O Hypertension, obesity and back pain treated with other muscle relaxants. Sudden death due to myocardial infarction on day he started cyclobenzaprine.
86090135	61yo/F	H/O Rheumatoid arthritis and coronary artery disease treated with multiple meds including cyclobenzaprine ≥ 1 year. Developed acute shortness of breath and died. Death was attributed to imipramine toxicity.
86090373	20yo/M	Developed muscle cramps S/P football practice. Treated with cyclobenzaprine and hydroxyzine. Died while being transported to a hospital. Autopsy revealed rhabdomyolysis, sickle cell trait, and acute hemolytic anemia.

Sponsor's Table 48 - WAES Reports of Cardiac Arrest, Ventricular Fibrillation, or Ventricular Tachycardia with Prescription Cyclobenzaprine

Fatal Outcome (Cont.):		
87040324	32yo/F	Hospitalized for depression and chronic pain treated with cyclobenzaprine, codeine, and barbiturates. Developed fever, rhabdomyolysis and suffered a cardiac arrest S/P 1-day treatment with doxepin and chlorpromazine. Died 29 days later due to hyperpyrexia.
88060670	Unk/M	H/O coronary artery disease. Died a sudden death after leaving ER S/P treatment with cyclobenzaprine for pain in the neck and upper extremity.
93030012	60yo/M	H/O Thyroid cancer and osteoarthritis treated with cyclobenzaprine, hydrocodone, and naproxen. Developed orthopnea. Died due to sudden death that was attributed to myocarditis.
Nonfatal Outcome:		
78100059	62yo/M	H/O Myocardial infarction, hospitalized due to chest pain, treated with cyclobenzaprine and diazepam, went into shock and cardiac arrest. Recovered and was discharged.
79020049	43yo/F	Developed syncope and cardiac arrest S/P second dose of cyclobenzaprine. Resuscitated and recovered.
80060084	Unk/M	H/O Treatment with cyclobenzaprine for 3 weeks prior to cervical laminectomy. Drug was stopped prior to surgery. Suffered a cardiac arrest during surgery and left comatose.
83060192	39yo/F	Hospitalized due to fever and myalgias secondary to mycoplasma infection. Treated with cyclobenzaprine and an antibiotic, developed documented heart block and cardiac arrest with complete recovery.
83080036	21yo/F	Hospitalized after developing abdominal pain S/P treatment with cyclobenzaprine. During exploratory laparotomy had an episode of ventricular tachycardia.
84030215	60yo/F	Suffered cardiac arrest following treatment with 1-dose of cyclobenzaprine S/P cervical laminectomy. Recovered.
96102303	59yo/F	S/P treatment with cyclobenzaprine > 1 year, fluoxetine, and other medications. Developed torsades de pointes intraoperatively after receiving droperidol. Prolonged QT interval noted before discharge.
97111397	20yo/F	Suicide attempt by overdosing with cyclobenzaprine, oxyprozin, and Methergine. Developed hypotension, tachycardia (SVT), and respiratory depression. Intubated. Treated with diltiazem, adenosine, cardioversion and physostigmine for resistant arrhythmia. Survived.

Digestive System:

The 3 most commonly reported adverse events associated with the digestive system were: nausea (37 cases), vomiting (18 cases), and dry mouth (16 cases).

(Refer to Sponsor's Table 45 shown above.) This is consistent with what was seen on review of the clinical trial safety data base discussed above. Cyclobenzaprine has anticholinergic effects which accounts for its ability to cause dry mucus membranes.

Hepatobiliary System:

As listed in the above table, Sponsor's Table 45, there were 20 case reports for hepatic function abnormality, 13 case reports for hepatitis, and 9 case reports for jaundice associated with the use of cyclobenzaprine. (Note: The 3 cases of hepatitis which resulted in individuals' deaths are not included in this section and are discussed above with the other deaths.) These 13 case reports of hepatitis and 9 case reports of jaundice are summarized in the following table, Table 49, created by this reviewer.

Table 49 - WAES Reports of Hepatitis and Jaundice Associated with the Use of Cyclobenzaprine

WAES No.	Age/ Gender	Synopsis
79020005	Unk/Unk	Hepatitis treated with cyclobenzaprine. Unknown cause of death.
81060121	Unk/Unk	Hepatitis due to misuse of cyclobenzaprine.
81090013	70yo/F	Developed facial rash and jaundice while taking cyclobenzaprine and butazolidin. Recovered.
81110037	21yo/M	H/O solvent exposure, treated with darvon and cyclobenzaprine developed jaundice. Liver biopsy suggestive of cholestatic drug reaction vs cholestasis due to viral hepatitis. Hepatitis screening for Hepatitis A and B both negative. Resolved with discontinuation of cyclobenzaprine.
82090262	27yo/M	Developed jaundice with serum bilirubin of 24 while being treated with cyclobenzaprine.
82100169	53yo/F	Treated with cyclobenzaprine and ibuprofen for muscle spasm. Developed jaundice, urticaria and hypersensitivity reaction. Hospitalized and recovered.
83020050	Unk/F	H/O prolonged treatment with cyclobenzaprine for low back pain. Developed hallucinations, cystitis, renal and liver disease. Hospitalized due to suicide attempt.
83080153	32yo/F	Treated with cyclobenzaprine and developed hepatitis.
85090540	Unk/F	Treated with cyclobenzaprine and Serax. Developed hepatitis and jaundiced. Hospitalized and recovered.
85110397	29yo/F	Treated with cyclobenzaprine, Tylox, ibuprofen and diazepam. Developed hepatitis and was hospitalized.
87030575	28yo/F	H/O gallstones. Treated with cyclobenzaprine, and erythromycin. Developed jaundice, pruritus, nausea and vomiting with right upper quadrant colicky pain. Hospitalized for intrahepatic cholestasis.

Table 49 (Cont.) - WAES Reports of Hepatitis and Jaundice Associated with the Use of Cyclobenzaprine

WAES No.	Age/ Gender	Synopsis
87060201	39yo/M	Treated with cyclobenzaprine, local corticosteroid injection and Nalfon for right hip pain. Hospitalized due to abdominal pain. S/P laparotomy found to have pancreatitis, jaundice and intestinal vascular insufficiency.
89010586	42yo/F	Intentional overdose with cyclobenzaprine. Had a seizure and developed jaundice.
90120728	30yo/F	Developed hepatitis following the intermittent use of cyclobenzaprine.
91040741	31yo/F	Treated with cyclobenzaprine and cimetidine. Developed hepatitis which resolved once the drugs were discontinued.
91200171	34yo/M	Treated with cyclobenzaprine, darvocet and medrol. Developed jaundice. Hepatitis screen negative for Hepatitis A, B, and C. Resolved after drugs were stopped.
93030269	37yo/M	Treated with cyclobenzaprine and indomethacin. Developed cholestatic jaundice and was hospitalized. Found to have intrahepatic lymphoma.
95020618	75yo/M	H/O renal insufficiency, heart murmur, TIA, S/P prostatectomy, and hernia surgery treated with cyclobenzaprine, aspirin, vitamin B-complex, and unknown skin preparation hospitalized with cholestatic hepatitis. Hepatitis viral screen all negative. Liver biopsy showed mild fibrosis with pericentral vein and triad inflammation with granuloma.
98071319	75yo/F	Treated with cyclobenzaprine, ibuprofen, diclofenac potassium, and nitrofurantoin. Developed nausea, vomiting, hypotension, tachycardia and abnormal liver function tests. Hospitalized due to drug induced hepatitis. Recovered following discontinuation of meds.

Eight out of the 19 cases listed in Table 49 developed hepatitis and/or jaundice while taking cyclobenzaprine which resolved after the drug was discontinued. The remaining 12 cases were confounded by other drugs that have been known to cause hepatotoxicity. Of the 20 cases of abnormal liver function, 7 were confounded by the concomitant use of other medications known to cause liver abnormalities (i.e., alcohol, acetaminophen, NSAIDs).

Immune System:

The most frequently reported adverse events associated with the immune system as shown in Sponsor's Table 45 were: hypersensitivity reactions (13 cases), allergy (12 cases), and drug allergy (10 cases). These case reports were requested but were received too late to be included in this review. The sponsor did submit 4 case reports of anaphylaxis which are summarized in the following table, Sponsor's Table 50.

Sponsor's Table 50 - WAES Reports of Anaphylactic Reactions Associated with the Use of Cyclobenzaprine

WAES No.	Age/ Gender	Synopsis
86060435	29yo/M	Treated with cyclobenzaprine and Nalfon. Hospitalized following an anaphylactic reaction and recovered.
89050415	57yo/M	Treated with cyclobenzaprine for muscle strain. Hospitalized due to an anaphylactic reaction (i.e., hypotension, rash, arrhythmia, and vertigo) and recovered.
90030376	51yo/F	Treated with cyclobenzaprine and tolmetin. Developed an anaphylactic reaction 12 hrs. after taking first dose of cyclobenzaprine (i.e., pruritus, rash, hypotension, dyspnea, and presyncopal episode). Post-recovery was rechallenged with cyclobenzaprine and developed the same symptoms. Tolmetin restarted without problems. (Note: This individual had taken cyclobenzaprine in the past without incident.)
95020177	37yo/F	Treated with cyclobenzaprine and ibuprofen for muscle sprain following an auto accident. Developed an anaphylactic reaction.

One of the 4 cases of anaphylactic reactions listed above (Case Report Number 90030376) is consistent with a positive dechallenge-rechallenge in an individual who had used cyclobenzaprine without incident previously. The current prescription labeling contains a warning that the drug not be used in individuals who are allergic to it.

Nervous System:

The 3 most commonly reported nervous system adverse events associated with the use of cyclobenzaprine listed in Sponsor's Table 45 were: somnolence (37), seizure/grand mal seizure (26), and headache (22). Four out of the 37 somnolence case reports were considered to be serious in nature. Table 51 created by this reviewer lists the 27 case reports of seizures associated with the use of cyclobenzaprine in non-overdose situations. (Note: One of these cases, Case Report Number 89010586, was found by this reviewer to be miscoded under jaundice and thus was not included with the original 26 cases of seizures listed in Sponsor's Table 45. For completeness it was added to the table.) Twenty-four of the 27 cases of seizures occurred in individuals who did not have a prior history of seizure disorder. Although many of the cases were confounded by the use of concomitant medications, there were 6 cases where cyclobenzaprine was the only medication used. (See Table 51 below). Two cases occurred after the administration of contrast media for a myelogram. There was 1 case report of a seizure which occurred in an individual who was also taking the analgesic tramadol whose prescription carries a warning regarding the potential for seizure activity when these drugs are taken concomitantly.

Table 51 - WAES Reports of Seizures Associated with the Use of Prescription Cyclobenzaprine

WAES No.	Age/ Gender	Synopsis
77110018	25yo/M	H/O Reiter's Syndrome. Treated with demerol. De novo seizure 4 days after starting cyclobenzaprine.
78120008	37yo/F	Hospitalized S/P back injury due to fall. Treated with physical therapy, valium and Robaxisal. Had a seizure after 5-days treatment with cyclobenzaprine. Questionable H/O abnormal EEG in the past due to head injury. Repeat EEG showed improvement off cyclobenzaprine.
78120154	Unk/Unk	Had a seizure while being treated with cyclobenzaprine.
79020053	22yo/M	Hospitalized for treatment of smoke inhalation and severe muscle sprain. Became lethargic and groggy after taking 1 dose of cyclobenzaprine and had a grand mal seizure.
7909127	75yo/M	Hospitalized with a spinal cord compression fracture. Treated with cyclobenzaprine for 2 days, became confused and had a seizure.
80030077	22yo/F	H/O Back pain and spasms. Treated with cyclobenzaprine for 1 week and had a grand mal seizure. Negative H/O seizures or use of other meds. EEG negative. No further seizure activity after cyclobenzaprine was stopped.
81040078	29yo/F	H/O Bradycardia treated with cyclobenzaprine and aspirin for low back pain for 3 days and had a gran mal seizure. PVCs with ventricular bigeminy and blocked PACs noted on cardiac monitoring. EEG positive for seizure activity.
82010029	51yo/M	Grand mal seizure following 1 dose of cyclobenzaprine. Seizure work-up unremarkable.
81100123	37yo/F	H/O Low back pain and thyroiditis. Treated with darvon, synthroid and cyclobenzaprine. After 3-days of treatment with cyclobenzaprine had a grand mal seizure. Work-up was negative.
83020281	Unk/F	Grand mal seizure after 3-days of treatment with cyclobenzaprine following the use of alcohol.
98012343	Unk/Unk	H/O Mental disorder. Had a seizure following treatment with cyclobenzaprine and tramadol. Seizures stopped when medications were discontinued.

Table 51 (Cont.) - WAES Reports of Seizures Associated with the Use of Prescription Cyclobenzaprine

WAES No.	Age/ Gender	Synopsis
97021334	47yo/F	H/O Depression, fibromyalgia, insomia, and suicidal ideation treated with cyclobenzaprine. Hospitalized S/P self-inflicted stab wounds during suicide attempt . Had grand mal seizure following surgery to repair wounds.
96101434	27yo/F	H/O Back pain treated with cyclobenzaprine while taking paroxetine, doxycycline, and tretinoin and had seizures. Seizure work-up was normal.
96060397	Unk/F	Poison control center report of seizures after starting cyclobenzaprine while taking amitriptyline and hyoscyamine sulfate (Levsin).
96050873	45yo/F	Generalized seizures S/P third bedtime dose of cyclobenzaprine.
94041003	63yo/F	Hospitalized for treatment of low back pain and sciatica. Treated with cyclobenzaprine, methocarbamol, demerol, ketorolac, promethazine, nifedipine and estrogens. Drugs were stopped over next 24-hrs.when patient became drowsy, unresponsive and seized.
94040024	Unk/Unk	Had a seizure after starting treatment with cyclobenzaprine.
93080764	Unk/Unk	Had a seizure after starting treatment with cyclobenzaprine.
92050039	79yo/F	H/O osteoarthrits, hypertension, low back pain, and hallucinations treated with cyclobenzaprine, atenolol, codeine, and acetaminophen prior to myelogram to R/O spinal stenosis. Had a gran mal seizure after myelogram with contrast media and sustained a fractured humerus.
89100797	Unk/Unk	Had a seizure after starting treatment with cyclobenzaprine.
88030685	Unk/M	Had a grand mal seizure following myelogram with contrast media while being treated with cyclobenzaprine.
87080182	50yo/M	Had a grand mal seizure after 1-weeks treatment with cyclobenzaprine and Motrin for muscle pain. Subsequent seizure work-up normal.
85020226	41yo/M	H/O seizure disorder controlled for 2 years on dilantin and phenobarbital. Had a seizure after 2-days treatment with cyclobenzaprine.
85020120	37yo/F	Developed seizures following 4-days of treatment with cyclobenzaprine, acetaminophen with codeine and ibuprofen for muscle spasm.
83090163	Unk/Unk	Had a seizure after ingestion of alcohol while taking cyclobenzaprine.
83050256	63yo/M	H/O spinal compression fracture and osteoporosis. Treated with Dolobid and cyclobenzaprine and developed seizures.
89010586	42yo/F	Intentional overdose with cyclobenzaprine. Had a seizure and developed jaundice.

Psychiatric Disorders:

Psychiatric disorders had the second highest number of postmarketing adverse events after body as a whole associated with the use of cyclobenzaprine. (Refer to Sponsor's Table 45.) The most commonly reported adverse events for this classification were: mental disorder (122 case reports), hallucination (80 case reports), confusion (27 case reports), disorientation (23 case reports), and psychosis (23 case reports). Twelve out of the 80 case reports of hallucination were considered serious and are listed in the following table, Table 52 created by this reviewer. Almost all were visual hallucinations which are more commonly seen due to drugs. Six of the cases summarized in Table 52 occurred in individuals $\geq$ 65 years of age.

Table 52 - WAES Reports of Hallucinations Associated with the Use of Prescription Cyclobenzaprine Considered to be Serious in Nature

WAES No.	Age/ Gender	Synopsis
79010036	70yo/F	H/O diabetes, breast cancer, and hypothyroidism. Hospitalized due to urinary retention, constipation, confusion S/P 2-days of treatment with cyclobenzaprine and sulindac. Condition improved. Died due to cardiac arrest.
98060608	77yo/F	H/O osteoarthritis and allergic rhinitis. Hospitalized after developing hallucinations after 3-days of treatment with cyclobenzaprine and codeine/acetaminophen for back pain.
92030649	40yo/F	H/O depression S/P auto accident treated with fluoxetine, bitartrate/acetaminophen and cyclobenzaprine for pain. Hospitalized due to hallucinations, disorientation and tachycardia which stop once meds were discontinued.
87070324	Unk/M	Treated with cyclobenzaprine for herniated disc and developed hallucinations and delusions.
87070265	Unk/F	Developed visual and auditory hallucinations, hyperactivity and insomnia after 1-days treatment with cyclobenzaprine.
86050182	36yo/M	H/O Multiple blood transfusions. Hospitalized for evaluation of hallucinations after taking cyclobenzaprine for 2 days. Died due to hepatic failure.
84110239	63yo/M	Hospitalized for evaluation of chest pains treated with cyclobenzaprine, sulindac, cimetidine with H/O peptic ulcer. Died due to GI bleed with hepatic failure.
83070005	29yo/M	Patient had been given prescriptions for cyclobenzaprine and corticosteroid. Death due to self-inflicted gunshot wound (suicide). At autopsy, cyclobenzaprine levels were undetectable.
83060279	80yo/M	Developed hallucinations and acute urinary retention while being treated with cyclobenzaprine.

Table 52 (Cont.)- WAES Reports of Hallucinations Associated with the Use of Prescription Cyclobenzaprine Considered to be Serious in Nature

WAES No.	Age/ Gender	Synopsis
83020050	Unk/F	H/O prolonged treatment with cyclobenzaprine for low back pain. Developed hallucinations, cystitis, renal and liver disease. Hospitalized due to suicide attempt.
82020086	70yo/M	H/O back pain treated with sulindac and cyclobenzaprine 60 mg/day. Developed confusion and was hospitalized. Died due to pulmonary embolism.
82020031	81yo/M	Hospitalized S/P fall and treated with cyclobenzaprine for muscle spasm. Developed hallucinations, confusion, and restlessness 2-days later and was readmitted. Improved once therapy was stopped.

Respiratory System:

As shown in Sponsor's Table 45, there were 14 cases of dyspnea associated with the use of cyclobenzaprine listed under the respiratory system. Sponsor's Table 53, shown below, summarizes the 5 serious case reports of respiratory distress. (Note: To avoid duplication, the deaths due to respiratory problems are listed in Sponsor's Table 46. These Case Report Numbers are: 82120185, 93030012, 95071757, 95121405, and 96091249.)

Sponsor's Table 53 - WAES Reports of Respiratory Distress Associated with the Use of Cyclobenzaprine

WAES No.	Age/ Gender	Synopsis
83110134	Unk/M	Received sodium pentothal during disc surgery, following which was treated with cyclobenzaprine and had a respiratory arrest 20 minutes after taking the latter. Successfully resuscitated.
85110341	36yo/F	Treated with butazolidin and cyclobenzaprine for neck pain. Developed dizziness, dyspnea, euphoria, dehydration, tachycardia, nausea and syncope. Hospitalized for treatment with IV fluids and cyclobenzaprine was discontinued. Discharged but continued to have hypotension for 2-3 days and then recovered.
86050437	40yo/F	S/P Treatment with cyclobenzaprine and Ibuprofen for low back pain developed dyspnea, severe muscle twitching and difficulty talking. Treated in ER with epinephrine and released. Muscle twitching sporadically persisted.
93030012	60yo/M	H/O Thyroid cancer and osteoarthritis treated with cyclobenzaprine, hydrocodone, and naproxen. Developed orthopnea. Died due to sudden death that was attributed to myocarditis.
95120870	64yo/M	H/O Hypertension, diabetes mellitus, osteoarthritis, pulmonary fibrosis, aortic aneurysm, prostatitis, labyrinthitis, and back pain treated with cyclobenzaprine, verapamil, naproxen, clonidine, theophylline, glyburide, metformin, and darvocet. Developed dyspnea, cough and chest pain. Hospitalized for treatment of congestive heart failure, dilated cardiomyopathy, and interstitial fibrosis.

Skin and Skin Appendages:

The 3 most commonly reported adverse events associated with the use of cyclobenzaprine for the skin and skin appendages were: rash (39 cases), pruritus (14 cases), and urticaria (13 cases). (See Sponsor's Table 45.) The severity of these reactions could not be ascertained since these case reports were received from the sponsor too late to be included in this review.

Urogenital System:

Sponsor's Table 45 lists 24 cases of urinary retention associated with the use of cyclobenzaprine. This is again due to the drug's anticholinergic effects. In addition, there were 15 case reports of the drug being used during pregnancy. These cases will be discussed below in the Usage in Pregnancy section.

Trauma:

Due to cyclobenzaprine's sedative effects, the sponsor also searched their data base for any reports related to trauma associated with the use of this drug. Seven (7) reports were identified and listed in Sponsor's Table 54. Although none of these reports were of automobile accidents in which the driver was taking cyclobenzaprine, there were 2 case reports (Case Reports Numbers: 95081896 and 97102255) in which drivers either concomitantly drank alcohol or took analgesics and were involved in accidents. Two (2) reports of injury (Case Reports Numbers: 83120194 and 89120204) involved elderly individuals ≥ 65 years of age who developed hallucinations and were injured in an accident or a fall. Sedation was not a factor in the remaining 3 cases. (See Sponsor's Table 54 below.)

Sponsor's Table 54 - Postmarketing Reports of Trauma Associated with the Use of Prescription Cyclobenzaprine

WAES No.	Age/ Gender	Synopsis
83120194	71yo/F	H/O Diabetes. Developed confusion and visual hallucinations after 2-days of treatment with cyclobenzaprine. Hit by a car after walking into the street.
87060484	Unk/M	Under treatment with cyclobenzaprine, drank alcohol in a bar and was killed in a bar fight.
88030685	Unk/M	Hospitalized after following a seizure S/P myelogram. S/P fracture of the humerus due to seizure.
89120204	87yo/F	Developed hallucinations S/P 2-doses of cyclobenzaprine and fell out of the bed injuring her back.
95081896	33yo/F	H/O Depression. Drank alcohol while under treatment with cyclobenzaprine and amitriptyline and was involved in a car accident.
97021334	47yo/F	H/O Depression and suicide attempts. Suicide attempt (stabbed herself) while on cyclobenzaprine.
97102255	Unk/M	H/O Chronic pain and depression. While under treatment with cyclobenzaprine and acetaminophen/propoxyphene developed psychosis, vandalized several homes, and drove his car into another car.

Use During Pregnancy/Fetal Exposure:

Cyclobenzaprine is a Pregnancy Category B drug and is not recommended for use in pregnant women. The sponsor searched its internal data base and identified 18 women that took cyclobenzaprine for a few days during 19 pregnancies. The outcomes of these 19 pregnancies are listed in Sponsor's Table 55. Since there was 1 pregnancy (Case Report Number : 93020514) that resulted in the birth of twins 20 outcomes are listed in Sponsor's Table 55. In 4 cases the outcomes were unknown.

Sponsor's Table 55 - WAES Reports of Pregnancy Outcomes Following Exposure to Cyclobenzaprine

Outcome	Number Of Cases	WAES Case Report Numbers
Unknown	**4**	91110383, 93010811, 94030942, 95070766
Live Birth/Normal	**5**	92020374, 92060295, 95020329, 96031473, 96051101
Live Birth/Congential Anomaly	**5**	79020050, 93020514, 95020563, 96032132, 96041594
Live Birth/Miscellaneous Adverse Outcome	**2**	88070041, 96082473
Abortion (Spontaneous or Elective)	**4**	93020514, 93120992, 95020329, 97010982

Although 5 babies were born with congenital anomalies as shown below in Sponsor's Table 56, there was no identifiable pattern to the anomalies. The 2 cases with miscellaneous adverse outcomes (Case Report Numbers: 88070041 and 96082473) resulted in a male infant with poor muscle tone at 8 months of age with no other neurological deficits, and a male infant with low blood sugar that resolved within 2 days after birth. The latter's mother also reportedly took chloroxazone, propoxyphene napsylate, ampicillin, erythromycin and acetaminophen during the course of the pregnancy.

Sponsor's Table 56 - Listing of Fetal Congenital Anomalies Reported to have Occurred Following In Utero Exposure to Cyclobenzaprine

WAES Case No.	Outcomes
79020050	Multiple external anomalies including short neck, disrupted lumbar spine, club feet, genital anomalies
93020514	Imperforate anus
95020563	Bone defect, umbilical cord abnormality, and syndactyly
96032132	Cleft lip and palate
96041594	Imperforate oropharynx, digital anomalies, costovertebral and auricular malformations; died at age 5 months

Literature Search

The sponsor also submitted the results of a literature search from 1965 to June 1, 1998 which identified information regarding the safety and efficacy of cyclobenzaprine. The literature data base for this submission contains 126 publications which can be found in abstract format in Attachment III at the end of this review. The

publications include case reports (25 references), the results of controlled clinical trials (16 references), new potential uses of cyclobenzaprine (46 references), general review (28 references), and articles about overdose experience with the drug (11 references).

The 25 case reports from the literature discussed occurrences of neuroleptic malignant syndrome, torsades de pointes, seizures, tinnitus, drug-induced hepatotoxicity, sciatic nerve irritation, drug induced delirium, syncope, and male sexual dysfunction associated with the use of cyclobenzaprine.

The 16 clinical trial articles describe a variety of efficacy studies in which cyclobenzaprine's effectiveness as a treatment for acute low back pain were studied. Ten out of the 16 references were trial reports; the remaining 6 were commentary reports. Four of the 10 references describe double-blind trials that compare cyclobenzaprine to other muscle relaxants. Three of these studies were double-blind placebo controlled trials, and 1 was an uncontrolled open-label study. Another 2 studies used analgesics concomitantly with cyclobenzaprine. Overall these studies found that cyclobenzaprine was efficacious to some degree in alleviating the symptoms of low back pain.

The 46 references, in which new uses for cyclobenzaprine are discussed, studied a variety of conditions: posttraumatic headache, depression, spasticity due to osteoarthritis, Parkinson's Disease, intractable pain syndrome and fibromyalgia. The numbers of patients enrolled in these studies were very limited. Although none of these studies reported any adverse events, the sponsor is presently not interested in pursuing any of the above indications.

Four out of the 28 general review articles discussed the potential increased risk for an adverse event associated with the prescription dose of 10-mg T.I.D. of cyclobenzaprine to occur in the elderly. The concern raised by these authors is that cyclobenzaprine is poorly tolerated in the elderly due to its anticholinergic side effects and its propensity to cause central nervous system toxicity in this age group.

Reviewer's Comments:

1. The safety profiles from the 1977 postmarketing study and the 1978 comparative study did not reveal any new or unexpected adverse events. Overall, the safety profiles from these 2 studies was similar to that of the safety data base generated from the 13 clinical trials conducted for this submission. (Refer to Sponsor's Table 44.)

2. Although the overall incidences of spontaneous postmarketing adverse event reports collected by the sponsor for prescription cyclobenzaprine was similar to that of the safety data base generated from the 13 clinical trials conducted for this submission, the sponsor did not query the FDA's Spontaneous Reporting System for other adverse event reports called in directly or associated with generic formulations. (See Sponsor's Table 45.) This information has been requested.

3. There were 14 sudden deaths in the postmarketing adverse event data base associated with the use of cyclobenzaprine which resulted in 9 deaths. Although many of these cases were confounded by underlying heart disease and other arrthythrogenic drugs, they can be explained by the fact that cyclobenzaprine is structurally similar to the tricyclic antidepressants which are known to cause cardiac arrhythmias. Thus, this drug should not be taken by individuals with known heart disease which is reflected in the current prescription labeling for this cyclobenzaprine. (Refer to Sponsor's Table 48.)

4. The incidence of drug-induced hepatitis associated with the use of cyclobenzaprine is relatively low based on the number of postmarketing adverse event reports submitted by the sponsor for review. (See Sponsor's Table 49.)

5. Use of cyclobenzaprine is known to be associated with anaphylactic reactions in susceptible individuals as seen by the information given in Sponsor's Table 50. The degree of magnitude and scope of allergic and hypersensitivity reactions associated with cyclobenzaprine is unknown, pending the completion of the review of postmarketing case reports submitted by the sponsor.

6. Use of cyclobenzaprine is known to be associated with the occurrence of de novo seizures. Concomitant use of cyclobenzaprine with other drugs can also increase the risk for seizure by lowering the seizure threshold in certain individuals. (Refer to Sponsor's Table 51.)

7. Based on postmarketing adverse event reports collected by the sponsor there is a risk for drug-induced hallucinations, confusion, disorientation and psychosis associated with the use of cyclobenzaprine. Elderly individuals $\geq$ 65 years of age may be at an increase risk for developing these psychiatric disorders. (See Sponsor's Table 52.)

8. Cyclobenzaprine is a Pregnancy Category B drug and is not recommended for use in pregnant women. The 20 postmarketing case reports of fetal exposure collected by

the sponsor do not lend support for reclassifying this drug at the present time. (See Sponsor's Tables 55 and 56.)

9. The sponsor's literature search reinforces the fact that the majority of cyclobenzaprine's toxicity focuses on the central nervous system. Thus, it may not be an appropriate drug for use in elderly $\geq$ 65 years of age.

Summary

In support of this prescription to OTC switch application, the sponsor has submitted the results of an actual use study in 468 individuals and a safety data base comprised of all the adverse events which were reported to have occurred to the 2,101 patients (1,632 of which received cyclobenzaprine) who participated in the 13 clinical studies contained in the submission. Although the results of this actual use study suggest that for the label tested the majority of patients ≤ 65 years of age could possibly safely use and tolerate this product, the limited time of the trial makes it difficult to determine if this is a true finding or one artifactually created by the protocol's self-limited duration. The study's limited length makes it difficult to determine if there exists a possibility for potential drug abuse and misuse. Safety concerns are also raised concerning this products use in the elderly and by other populations of consumers at risk for developing drug-drug interactions or metabolic side effects which were not adequately represented in this study. The failure to heed the warning not to drive while taking this medication is particularly worrisome in view of the product's potential for sedation and other centrally-mediated side effects.

The safety information generated from the studies in this submission are consistent with what is already known about the safety profile of the 10-mg dose of cyclobenzaprine, and does not reveal any new potential side effects associated with the use of this drug at lower doses. The most frequently reported adverse events in the clinical trial data base were somnolence, dry mouth, headache, asthenia/fatigue, nausea, and dizziness, the majority of which appear to be dose-dependent. Although post hoc analysis of gender-related adverse events failed to reveal any differences, there were insufficient numbers of elderly patients ≥65 years of age, and limited representation of ethnic minorities enrolled in the studies to support any meaningful conclusions regarding cyclobenzaprine's safety profile in these subpopulations. The only information regarding drug-drug and drug-disease interactions associated with cyclobenzaprine was generated by post hoc analysis of patient's who were taking background analgesics, or who reported worsening of an underlying medical condition. Thus, no definitive pharmacodynamic information was generated by this safety data base which could be included in the product's consumer labeling regarding warnings of potentially hazardous drug and disease interactions which could occur while taking cyclobenzaprine.

The sponsor also submitted for review an analysis of 968 postmarketing adverse event reports collected by their own worldwide safety monitoring data base and a review of the literature. Sixty-six (66) out of these 968 adverse event reports were attributed to drug overdoses with cyclobenzaprine and are discussed with the overdose information collected by the Toxic Exposure Surveillance System (TESS) operated by the American Association of Poison Control Centers (AAPCC) contained elsewhere in this review. Of the remaining 902 adverse event reports, 186 were coded for serious adverse events associated with the use of cyclobenzaprine such as seizures, tachycardias and arrhythmias, hallucinations, and psychosis. There were also 51 case reports of deaths associated with the use of cyclobenzaprine, 12 of which were due to accidental or intentional overdoses with the drug. Eight deaths occurred in patients ≥

65 years of age, while 5 were reports of fetal death due to intra-utero exposure to cyclobenzaprine. The majority of the deaths were due to underlying medical conditions such as heart disease or the concomitant use of other drugs such as alcohol and other central nervous system depressants, monoamine oxidase inhibitors, and other tricyclic antidepressants. (Note: Although the sponsor supplied a review of the postmarketing adverse events it had collected internally, they did not query the agency's Spontaneous Reporting System for any additional deaths or serious adverse event reports related to generic bioequivalents of their drug or those that might have been called in directly to the Medwatch system. This information has been requested and is currently under review.) The issue of the 13 sudden deaths and the other nonfatal cardiac events in individuals who took cyclobenzaprine is worrisome to this reviewer. Although the overall incidence is small and most of these cases occurred in individuals with other risk factors for heart disease and cardiac events, their number may be limited by the judicious use of this drug by health care providers in susceptible populations. Once this barrier is lifted, the incidence of sudden death may increase associated with the availability of this product.

Although cyclobenzaprine itself has been known to cause seizures (27 postmarketing case reports), review of the literature reveals 4 cases of seizures with the concomitant use of this drug with tramadol. This has resulted in a warning statement regarding the concomitant use of both drugs on the prescription label of tramadol. Review of the literature also reveals reports of hyperpyretic crisis and deaths associated with the use of cyclobenzaprine and monoamine oxidase inhibitors. In addition, there is published literature regarding the poor risk-benefit ratio of this drug in the elderly who are at increased risk for developing adverse events related to the drug's anticholinergic effects and central nervous system toxicity. The latter is supported by the high number of postmarketing reports in the elderly for neurological and psychiatric disorders associated with the use of cyclobenzaprine.